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THE DIAGNOSIS OF CARCINOMA OF THE COLON AND RECTUM*

A REVIEW OF 714 CASES

BY E. G. MUIR, LONDON

THE classical signs of this disease are stated to be alteration in bowel habit, pain, and the passage of blood. These are undoubtedly correct, but blood may pass unnoticed, pain be ascribed to other ills, and 'alteration in bowel habit' is a phrase unknown to patients. Yet it should be emphasized that much of the patient's future depends on clinical diagnosis and not on the laboratory aids. He seeks advice first from his practitioner. If *his* suspicions are aroused by the story and the clinical signs, he refers the patient to hospital: if they are not, perhaps a lethal delay takes place.

In this series of 714 cases there were 109 patients with carcinoma of the right colon (cæcum, ascending colon, and right half of transverse colon), 74 with carcinoma of the left colon, 114 with carcinoma of the sigmoid, and 417 with carcinoma of the rectum and rectosigmoid. Many of the clinical signs are common to all, but there are features more marked in one site than the other, and it is convenient to consider them in these groups. The patients we are considering are all those suffering from malignant disease of the colon and rectum admitted to a group of some 650 general hospital beds located in three different hospitals over a 10-year period from 1945 to 1955. All cases are included, whether admitted for surgery or for investigation in a medical ward for ascites, anæmia, or enlarged liver. I have attempted to analyse the frequency of the different symptoms and the main physical signs relevant to the disease which were present on the patient's admission to hospital. The duration of the symptoms has been noted and also those cases in which undue delay occurred in diagnosis or investigation.

THE RIGHT COLON

(109 *Cases, Table I*)

Abdominal Pain.—This was quite the most common symptom given by the patients and was present in 85 cases (78 per cent). In addition it was the most prominent symptom in well over two-thirds of these patients. The pain was frequently described as colicky or griping in character and sometimes as a dull ache in the right side. In one-third of the cases pain followed or was brought on by taking a meal, and in others such a relationship was implied by statements such as "afraid to eat". The pain was usually "all over the abdomen" when it occurred, or in the right side, and in only 1 case was it described as epigastric.

Loss of Weight.—This was the next most frequent complaint that featured in these patients' case histories. It was stated by the patient in almost half the number, 53 cases (48·6 per cent), though no doubt in many of them the complaint was obtained by questioning.

Vomiting.—This complaint was third in frequency, being present in about one-third of the patients (32 per cent), and this figure does not include patients admitted to hospital with acute intestinal obstruction. It was described as an occasional vomit or as an attack of vomiting lasting some twenty-four hours and frequently associated with colic.

Alteration of Bowel Habit.—Diarrhœa was present in 23·8 per cent and constipation in 22 per cent, and many patients (30 per cent) had experienced both; some stated that they had attacks of pain, vomiting, and diarrhœa.

Anorexia.—Loss of appetite was mentioned by 20 patients (18·3 per cent), but in only 2 cases was it given prominence in the story. In some cases the patient had been "afraid to eat".

Faintness, Weakness, Lassitude, or Breathlessness.—Faintness and lassitude were present in 19, breathlessness in 15 cases. One of these symptoms, or a combination of them, was given as a first symptom by 21 patients, nearly 20 per cent of the whole, and, unlike anorexia, when it was present it was a prominent feature in the patient's story.

On admission 23·8 per cent of patients had a blood hæmoglobin below 70 per cent, 8·2 per cent a level below 50 per cent, and in 6·4 per cent it was below 40 per cent. Though there was no exact relationship between symptoms and hæmoglobin level, there were no patients with levels below 40 per cent who did not complain of these symptoms.

Indigestion.—This was noted as a complaint in 14 cases (8·2 per cent).

Palpable Mass.—In 12 cases, 11 per cent of the whole, the patients were not admitted to hospital until they themselves had noticed a lump in the right side of the abdomen and drawn the attention of the doctor to it. It was sometimes stated that the lump varied in size. On their admission to hospital a

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palpable mass was present in the right side of the abdomen in 74 out of 109 cases (67·7 per cent), that is over two-thirds of all cases. Since the average duration of symptoms was almost six months, it is disturbing to reflect that it needed a palpable mass in the abdomen before most of the cases could be diagnosed. However, only a slightly lower percentage has been given recently by an American review,

Table I.—Carcinoma of Right Colon—Symptoms and Signs

	Per cent
Abdominal pain (In one-third related to food)	78
Loss of weight	48·6
Vomiting (Frequently with colic)	32
Bowel complaint	30
Anorexia ("Afraid to eat")	18·3
Faintness, breathlessness	20
Indigestion	8·2
Acute obstruction	8·2
Mass present	67·7
Bleeding	8·2

where 55·4 per cent of patients with carcinoma of the right colon had a palpable abdominal tumour on their admission to hospital (Shallow, Wagner, and Colcher, 1955).

Acute or Complete Obstruction.—This was present in 9 cases (8·2 per cent) of carcinoma of the right colon on their admission to hospital.

Other Complaints.—Distension of the abdomen was noted by 11 patients (excluding those admitted with acute obstruction); bleeding in 9 (8·2 per cent); nausea, as distinct from vomiting, in 6; borborygmi in 3; fever in 2; pallor, noted by friends or relatives, in 2; jaundice in 1 case. One patient attended hospital complaining of an ulcer in the right groin which was found to be a metastasis in an inguinal gland; 1 with pain in the chest due to secondary deposits; 1 with an ulcerated umbilicus containing growth, and 1 with œdema of both legs.

Duration of Symptoms.—The average duration before admission to hospital was 5·5 months, the range being between four years and a few days. The presence of a long history in bowel carcinoma tempts one to doubt its accuracy but, though four years is exceptional, two years was not uncommon. It is, of course, quite probable that in some of these cases the tumour producing the symptoms was initially benign.

While post-operative prognosis is not considered here, it may be of interest to point out now that a short history before admission to hospital is not necessarily associated with a good post-operative prognosis. For the right colon the average duration of pre-operative symptoms in those surviving five years after resection was 10·7 months; in those surviving three years it was also 10·7 months, and in those cases found to be inoperable at laparotomy it was only 5·6 months. Naturally we cannot take this to mean that a patient with carcinoma of the colon will benefit from delay in admission to hospital. It almost certainly does mean that a shorter history may indicate a more rapid and malignant growth, while the longer histories may include some tumours which were originally benign. The patient giving the longest pre-operative history of four years had a large, bulky tumour of the cæcum without gland involvement and a hæmoglobin level of only 38 per cent, but he survived over five years after his operation, to die of cardiac failure and acute bronchitis at the age of 76.

Before we consider the pattern of symptoms which emerge from the clinical histories of these patients I will describe briefly some of the cases in which mistakes were made by the practitioner and by the hospital. Out of 109 cases of cancer of the right colon, there were 28 in which errors and mistakes in diagnosis caused considerable delay in treatment. No doubt there were more, but the history was not sufficiently informative. In addition there were 2 cases where delay in hospital appointments, investigations, and admissions culminated in the patient's admission with complete obstruction (*Table II*).

These stories are a little repetitive, but I hope that they create some sort of picture. It would seem that it is not easy to make an early diagnosis of carcinoma of the right colon, but certain features are suggestive of it and certain difficulties common to it.

Pain is a common feature with carcinoma of the right colon and it tends to be felt either as small intestinal pain, with a definite relationship to the ingestion of food, or as pain in the cæcal and appendicular region. Both may be present. With the first there is a danger that it will be confused with a peptic ulcer or regarded as 'gastric', though the pain is not really epigastric in its site. With the second, the appendix may be suspected or even removed. In this group there were 5 cases in which a diagnosis of appendicitis was made, and in 3 the appendix was removed without recognition of the growth. There were 2 other cases, not included, in which the same diagnosis was made but corrected in time to avoid disaster. The carcinoma of the colon appendix is a well-recognized danger. Back-pressure in the cæcum is transmitted to the appendix and pain is experienced. When the appendix is delivered through a gridiron incision, it may look distended and infected and it is not difficult to regard it as the cause of pain. In some cases it may be genuinely inflamed.

Vomiting is quite a frequent symptom and its presence seems unfortunately to persuade some of us that the lesion must be gastric. Attacks of vomiting in an elderly patient are almost as likely to be due to a carcinoma of the right colon as a gastric or duodenal ulcer. Anæmia, pain, and a positive occult blood always lead to investigation, but here further difficulties may be encountered. Duodenal scarring is probably not an uncommon finding, and if it is discovered by a barium meal it may lead to prolonged rest and a milk drip. I have formed the impression that to order a barium meal *alone* for an elderly patient with abdominal pain that is not quite clearly gastric or duodenal can be a dangerous proceeding and that it can become still more dangerous if a follow-through is carried out. A positive finding is of value provided it is the right lesion that is found: a negative finding may give a dangerous assurance. A barium enema is also required. It is much more accurate in the diagnosis of colonic lesions and much less likely to precipitate the complete obstruction that may follow a barium meal.

A positive occult blood is an important finding, but if the patient has also duodenal scarring it does not always mean that they are associated. Anæmia with a growth of the right colon is a text-book picture, as are also constipation and diarrhœa, yet these signs were often missed, or if recognized were not related to the cause. Fatigue, pain, or loss of

weight in an elderly subject always calls for the exclusion of cancer.

Table II.—Carcinoma of Right Colon—Cases with Undue Delay in Diagnosis

Case and Sex	Age	Details
R. A. F.	59	Referred to hospital with epigastric pain, occasional vomiting, shortness of breath and diarrhœa. Hb 46 per cent. Treated for 7 months as anæmia and 'anginal' pain. Finally mass felt
H. B. F.	43	Hospital sister. Previous history of ulcer. Treated for 4 months for pain after meals and occasional vomiting. Finally patient felt mass and informed doctor
E. B. F.	66	Attack of pain and nausea regarded by practitioner as appendix abscess. Mass seemed to get smaller. Two months' delay
D. B. F.	58	Attack of pain and vomiting for which appendix was removed. Continued to get attacks of pain and vomiting. Regarded as cholecystitis. Cholecystogram normal. Referred to psychiatrist. Patient left her doctor and went to a different hospital. Seven months' delay after appendicectomy
S. B. M.	61	Pain, vomiting, and loss of weight. Doctor arranged a barium meal which was normal. Treated for dyspepsia for 4 months. Patient noticed lump in R.I.F. and informed doctor
F. C. M.	70	Treated by doctor for 9 months for anæmia. Loss of weight and pain ascribed to gastric flu
A. C. M.	72	Treated by doctor for 6 months for 'gall-stone colic'. Mass felt, but regarded as gall-bladder
L. D. F.	73	Attended hospital out-patients for 2 years for pain, vomiting, and loss of weight. Barium meal normal. Finally mass felt in R.I.F.
F. F. M.	73	Investigated for faintness, loss of weight, and anæmia. Positive occult blood. Barium meal suggested duodenal ulcer. Treated for 9 months before correct diagnosis
E. G. F.	57	Treated 4 months for indigestion. Then had barium meal and follow-through and cholecystogram. All normal. Treated for a further 2 months. Then mass felt
N. G. M.	68	Suffered from indigestion, pain, and attacks of diarrhœa for about 1 year. Patient himself was a doctor. Admitted with complete obstruction
M. H. F.	73	Treated by doctor for 2 years for shortness of breath. Regarded as bronchitis. Later mass felt and patient found to be very anæmic
F. H. M.	46	Treated by doctor for 5 months for indigestion. Barium meal was normal. Later barium enema showed growth
M. H. F.	70	Appendicectomy for pain in the R.I.F. Pain persisted and 5 months later mass felt in R.I.F.
E. H. F.	68	Admitted for melæna to hospital, with indigestion, faintness, and diarrhœa. Hb 49 per cent. Barium meal: doubtful duodenal ulcer. Treated for 2 months in hospital. Then barium enema showed growth
R. H. F.	65	Treated for 8 months in hospital out-patients for pain after meals, flatulence, and diarrhœa. Barium meal normal. Later mass felt and thought to be palpable gall-bladder
C. L. F.	74	Two years previously attack of pain and swelling in R.I.F. Regarded by doctor as subsiding appendix abscess. Continued with repeated attacks of 'appendicitis', but operation not advised because of age
M. L. F.	69	Vomiting and diarrhœa regarded for 2 months as 'nervous debility'
A. P. F.	59	Treated by doctor for 9 months for anæmia. Hb 44 per cent
L. P. M.	71	Treated by doctor for 2 years for anæmia, breathlessness, giddiness, pain after meals, and vomiting
E. R. F.	62	Attended hospital with pain after meals, borborygmi, and occasional vomiting. Barium meal normal. Later repeat barium meal showed hiatus hernia (?) with ulcer. Admitted and treated by milk drip. Gastroscopy: N.A.D. Finally mass felt. Six months' delay under hospital care
S. S. M.	56	Regarded for 9 months in hospital out-patients as a post-gastrectomy syndrome. Then mass felt in R.I.F.
E. S. M.	79	Treated by doctor for 4 months for pain and vomiting. 'Gastric'
A. S. F.	63	Treated for 3 months for flatulence, vomiting, and pain. Regarded as 'gastric'
J. T. M.	67	Attended hospital out-patients with pain and constipation. Barium enema normal. Under hospital observation for 18 months and finally mass felt in R.I.F.
E. T. F.	68	Admitted to hospital for chronic bronchitis, breathlessness, and microcytic anæmia. Under hospital care for 18 months. Then admitted with complete obstruction
P. T. [illegible]	52	Appendicectomy for supposed acute attack. Appendix noted as normal. Continued with pain and nausea for 5 months, when barium enema showed carcinoma
F. W. A.	76	Treated by doctor for indigestion for 4 months

It may be thought that the mistakes and errors in this series are so frequent that it must be unusual. However, the 5-year survival rate here is the same as that given by Grinnell (1953) and I have no reason to suppose that these cases are in any way exceptional.

THE LEFT COLON

(74 *Cases, Table III*)

While there is no sharp distinction between the symptoms from right and left colonic growths, there is a change in their relative frequency.

Pain.—This is still the most common symptom, being present in 51 cases (68·9 per cent), but while at least one-third of all cases with right colon growths had noticed that the pain was related to meals, only 2 patients with left colon growths made this complaint.

Table III.—Carcinoma of Left Colon—Symptoms and Signs

	Per cent
Abdominal pain (Only 3 per cent related to food)	68·9
Bowel complaint	58
Acute obstruction	21·6
Loss of weight	14·8
Vomiting	14·8
Bleeding	9·4
Faintness, breathlessness	9·4
Anorexia	9·4
Mass present	45·9

Alteration of Bowel Habit.—With the left colon this now becomes the second most frequent complaint. Constipation was present in 30 (40·5 per cent), diarrhœa in 18 (24·3 per cent), and either one or the other or both were present in 43 patients, 58 per cent of the whole.

Loss of Weight.—Now presents in 11 out of 74 patients (14·8 per cent). A less frequent complaint than on the right side.

Vomiting.—Excluding those with complete obstruction, this was a complaint in only 11 cases (14·8 per cent), less than half its frequency with the right colon.

Complete Obstruction.—This was much more common on the left side than the right, no less than 16 patients (21·6 per cent) being admitted in this state. One case followed a barium meal.

Palpable Mass.—Noticed first by the patients in 6 cases (8·1 per cent) and on admission to hospital a mass could be felt in 34 cases (45·9 per cent). The diminished frequency, compared with the right colon, may be attributable to the difficulty in palpating the splenic flexure.

Lassitude and Breathlessness.—These were also less prominent on the left side. Lassitude (6) and breathlessness (1) were present in 7 cases (9·4 per cent). On admission 13·5 per cent of patients had a blood hæmoglobin below 70 per cent, 8·1 per cent a level below 50 per cent, and 1 patient a level below 40 per cent.

Anorexia.—This was a complaint in 7 cases (9·4 per cent), half the frequency of the right side.

Bleeding.—This had been noticed in 7 cases (9·4 per cent), about the same frequency as on the right side.

Other Complaints.—Borborygmi had been noticed by 6 patients, distension (excluding obstruction) by 1 patient.

Peritonitis.—Two patients were admitted with peritonitis, through perforation of the site of growth, and 1 patient was admitted with a local abscess.

Duration of Symptoms.—The average duration before admission to hospital was 5–6 months, the range being between two years and a few days. Although the duration of symptoms before admission to hospital was the same, in the left colon there does not seem to have been quite the same number of 'characteristic' errors in diagnosis as with the right, and I think this is attributable to the manner in which right colonic growths can mimic gastric or appendicular symptoms (*Table IV*).

Table IV.—Carcinoma of Left Colon—Cases with Undue Delay in Diagnosis

Case and Sex	Age	Details
C. R. F.	62	Treated by doctor for 3 months with antibiotics for urinary infection. Later mass felt. Patient had vesicocolic fistula from carcinoma of transverse colon
I. H. F.	50	Treated by doctor for pain in left side for one year. Eventually mass felt
E. K. M.	63	Investigated by barium enema for pain and diarrhœa. Diverticulitis shown. Admitted to hospital 18 months later with inoperable carcinoma of descending colon and ascites
R. B. F.	53	Treated by doctor for constipation for 6 months until mass felt
C. W. F.	47	Had carcinoma of sigmoid resected 18 months before. Later mass felt in epigastrium and regarded as secondary in liver. Treated with X-ray therapy elsewhere. Six months later explored, when mass proved to be another primary carcinoma of the transverse colon which was still operable
D. R. M.	60	Initial complaint of pain produced a barium meal. This showed a chronic duodenal ulcer. Treated in hospital out-patients for 3 months until admitted with complete obstruction.

It will be seen that diverticulitis is beginning to appear in the differential diagnosis and that once again radiological findings, though perfectly accurate, attracted attention from the real lesion.

THE SIGMOID COLON

(114 *Cases, Table V*)

Alteration of Bowel Habit.—This was quite the most frequent complaint in cases of sigmoid carcinoma. Of the 33 patients who were admitted with acute obstruction, 16 gave a previous history of constipation, 4 of diarrhœa, and 2 of both. The remaining 11 cases had apparently only noticed constipation for the few days preceding admission. Of the remaining 81 cases—not admitted in obstruction—22 complained of constipation, 21 of diarrhœa, and 16 of both. In all, 80 out of the 114 patients (70·1 per cent) had suffered from sufficient bowel disturbance to complain of it.

Pain.—Often colicky; sometimes described as a dull ache and usually present in the lower abdomen. This was present in 58 cases (50·8 per cent). It is difficult to believe it was absent in the remainder, but it was not given as a complaint on admission, possibly because it was overshadowed by other symptoms.

Acute Obstruction.—While hardly a symptom, this has now become one of the more common presentations of the case. Almost one-third of the patients with sigmoid carcinoma (33 patients, 28·9 per cent) were not admitted to hospital until they were completely obstructed, a figure considerably higher than in the other parts of the colon. The duration of previous symptoms given in this group is interesting, though possibly the condition under which they were admitted did not make for accuracy.

3	patients	gave a previous history of	1 year or more
4	,,	,,	6 months
2	,,	,,	4 months
2	,,	,,	3 months
11	,,	,,	1 week to 1 month
11	,,	,,	a few days

Bleeding.—With sigmoid growths this is now third in frequency, being noticed by 33 patients (28·9 per cent).

Loss of Weight.—This was a complaint in 23 cases (20·1 per cent).

Table V.—Carcinoma of Sigmoid Colon—Signs and Symptoms

	Per cent
Bowel complaint	70·1
Abdominal pain	50·8
Acute obstruction	28·9
Bleeding	28·9
Loss of weight	20·1
Breathlessness, faintness	6·1
Vesicocolic fistula	6·1
Mass present	38·6
Peritonitis and abscess	10·4

Distension.—Excluding obstruction, it was a complaint in 11 cases (8·6 per cent).

Breathlessness and Lassitude.—Together these were present in 7 cases (6·1 per cent).

Urinary Symptoms.—Seven patients were admitted with a vesicocolic fistula (6·1 per cent). In 5 there were specific symptoms referable to it, such as pneumaturia, hæmaturia, frequency, or dysuria. In 2 no complaint relative to it was noted.

Palpable Mass.—This had been noticed by the patient on only 3 occasions, but at the time of admission to hospital it was noted that a mass could be felt on abdominal examination in 21 cases; on rectal examination in 27; and by one or other examination in 44, 38·6 per cent of the whole. This is naturally a lower figure than the rest of the colon, but quite a high proportion were detected on rectal examination.

Other Complaints.—The passage of mucus had been noticed by 7 patients, a complaint not apparently mentioned by patients with growths of the right and left colon. Nausea was present in 6 cases, anorexia in 5, vomiting (excluding cases of obstruction) in 4, flatulence in 2, tenesmus in 2, and borborygmi in 1 case.

Peritonitis and Abscess.—Unfortunately this showed a sharp rise in frequency with growths of the sigmoid colon. Eight patients were admitted with peritonitis, 7 from the perforation of a sigmoid carcinoma and 1 from perforation of the cæcum in a case of complete obstruction from a sigmoid growth. Four patients were admitted with a localized abscess around the growth. In all, 12 patients (10·4 per cent) were admitted with local or general peritonitis.

Duration of Symptoms.—The average duration of symptoms was 6·5 months.

With growths of the sigmoid colon interference with bowel habit had become sufficiently marked to make it a complaint with over two-thirds of the cases; almost one-third suffered from bleeding and almost one-third were admitted to hospital with acute obstruction. One case in every ten was admitted with either peritonitis or a local abscess.

As far as errors in diagnosis by the practitioner are concerned, I think we would all agree that to treat any elderly person who is suffering from constipation, diarrhœa, or the passage of blood or anæmia or abdominal pain without investigation is a hazardous proceeding. The errors in diagnosis made in hospital were frequently due to an incomplete investigation of the alimentary tract, which revealed either the wrong lesion or no lesion and gave an assurance that was disastrous (*Table VI*).

Table VI.—Carcinoma of Sigmoid—Cases with Undue Delay in Diagnosis

Case and Sex	Age	Details
K. C. F.	57	Treated by doctor 3 months for anæmia and constipation
H. C. M.	68	Treated by doctor 3 months for pain in lower abdomen, relieved by micturition. Attended hospital. X rays showed gall-stones and cystoscopy diverticulum of bladder. Finally admitted in complete obstruction with inoperable growth
M. B. F.	67	Treated by doctor 6 months for constipation
A. F. M.	58	Admitted hospital after barium meal and follow-through suggested chronic D.U. Anæmic; Hb 35 per cent. Discharged 10 months later. Readmitted 2 months later with complete obstruction and inoperable growth
S. F. M.	76	Treated by doctor 2 months for gastric ulcer. Had carcinoma of sigmoid with liver metastases
G. P. M.	62	Constipation and diarrhœa. Patient and doctor reassured after sigmoidoscopy. No barium enema. Admitted 8 months later with complete obstruction
E. P. F.	69	Treated at hospital for cystitis for 7 months. Later vesicocolic fistula discovered
F. R. M.	51	Treated by doctor for piles. Bleeding continued. After 18 months periodic treatment vesicocolic fistula developed
C. W. M.	69	Doctor thought he felt mass in pelvis. Referred to hospital, where sigmoidoscopy N.A.D. barium enema, diverticulitis. Readmitted 5 months later with inoperable growth
G. B. M.	76	Attended the out-patients of a hospital for 9 months for diarrhœa, which he was told was due to a "nervous bowel". Inoperable growth
A. E. M.	57	Admitted to a hospital for 4 months for "weakness after flu" and anæmia. One month after discharge readmitted with inoperable growth
H. M. F.	74	Admitted to a hospital for cystitis. Discharged. Re-admitted 5 months later with vesicocolic fistula
A. P. M.	60	Had suffered from ulcerative colitis 3 years. Bleeding became more marked. Sigmoidoscopy N.A.D. Piles injected. Six months later admitted with inoperable carcinoma sigmoid
J. D. M.	63	Treated by doctor 9 months for diarrhœa, blood, and mucus
A. C. M.	55	Treated by doctor 3 months for "gastro-enteritis"
V. T. F.	27	Under treatment at hospital as "ulcerative colitis". After 3 months mass felt in abdomen
E. W. F.	64	Treated by hospital for 6 months as diverticulitis after barium enema failed to show growth
W. N. M.	61	Appendicectomy through gridiron incision for peritonitis. Death 2 days later. Post-mortem showed perforated carcinoma of sigmoid

Differential Diagnosis from Diverticulitis.—Although I have only quoted two cases in which diverticulitis was confused with carcinoma, it is a problem which constantly recurs. The area is one in which both diseases are common: they both occur in the same age group and the presence of the first is no bar to the development of the second. Differences in the clinical picture, each one of little significance, may in their sum total assist in the differential diagnosis.

History.—This is usually longer in diverticulitis and may contain periods of remission.

Type of Patient.—Obesity seems to be associated with diverticulitis. Loss of weight was present in 20 per cent of sigmoid carcinomas.

Pain.—A complaint in both, but perhaps more marked in diverticulitis.

Pyrexia.—Recurrent attacks of pain and pyrexia are more suggestive of diverticulitis.

Alterations in Bowel Habit.—These occur in both, but are more marked in carcinoma.

Bleeding.—This occurs in perhaps 20 per cent of cases of diverticulitis, but as a persistent complaint it is more marked in carcinoma. Colcock and Sass (1954) quote 64 per cent of patients with carcinoma as passing blood, compared with 22 per cent of those with diverticulitis, though the percentage of carcinoma with bleeding was not so high in this series. Massive exsanguinating hæmorrhage may occur in diverticulitis and is uncommon in carcinoma. Bleeding in diverticulitis may be either from congested mucosa in a narrowed area or from granulations in a diverticula, but if it does not improve rapidly under conservative measures carcinoma should be suspected.

Palpable Mass.—This may be present in both, but a large tender mass in a fit patient suggests diverticulitis and in an ill patient carcinoma.

Sigmoidoscopy.—This may reveal a growth.

Barium Enema.—The diagnosis is usually made on this investigation:

Differential Diagnosis

Carcinoma	*Diverticulitis*
Filling defect	Narrowed area
Sharp edges	Saw-toothing spasm
	Tails off
Short distance	Several inches
Mucosa destroyed	Mucosa intact
Appearances constant	Appearances vary
	Improves with antispasmodics
	Diverticula

In the great majority the radiological diagnosis is easy: in some it is difficult, and in a few it is impossible. The rectosigmoid is notoriously a difficult region.

Cytology.—While the value of cytologic diagnosis in malignant disease of the uterus is established, its place in malignant disease of the bowel is regarded by some as experimental, by others as a valuable aid in differential diagnosis. Bader and Papanicolaou (1952) reported 19 cases of cancer of the colon and rectum where a positive diagnosis of malignancy was made on bowel washings in 18. In the remaining case a benign polyp was diagnosed and subsequent histology proved this to be malignant. McAmmond (1955) has discussed the problem from the surgical standpoint and considers cytologic diagnosis as likely to increase its value. All accounts stress that it is a method which requires careful training, both of technicians and pathologist, and that only an experienced team will produce results that are of value.

When X-ray and other evidence fails to establish a certain diagnosis, laparotomy is essential. Lloyd-Davies (1953) has pointed out the value of introducing a sigmoidoscope during the laparotomy with the patient in the lithotomy-Trendelenburg position and threading it through the affected area after the loop has been freed. If at laparotomy it is still impossible to make a certain diagnosis, resection should be performed: in any case it is probably the best treatment for a case of diverticulitis with sufficient induration to mimic carcinoma.

THE RECTUM AND RECTOSIGMOID
(417 *Cases*)

Alteration of Bowel Habit.—Eighty-one per cent of patients in this group made some complaint about their bowel habit, 54 per cent of diarrhœa,

Table VII.—Carcinoma of Large Bowel—Site and Symptoms

Symptom	Right Colon	Left Colon	Sigmoid	Rectum
	Per cent	*Per cent*	*Per cent*	*Per cent*
Pain	78	68·9	50·8	5
Bowel complaint	30	58	70·1	81
Vomiting	32	14·8	3·5	—
Bleeding	8·2	9·4	28·9	66
Weight loss	48·6	14·8	20·1	28
Faintness, lassitude	20	9·4	6·1	—
Acute obstruction	8·2	21·6	28·9	3·5
Abscess peritonitis	1	2·7	10·4	—
Mucus	—	—	6·1	22
Tenesmus	—	—	—	15
Mass	67·7	45·9	38·6	—

31 per cent of constipation, and a considerable number of both.

Bleeding.—This was the most frequent single complaint (66 per cent).

Loss of Weight.—Present in 28 per cent. Personally I did not expect to find it so commonly noted with carcinoma of the rectum.

Mucus.—This was now a complaint in 22 per cent.

Tenesmus.—Present in 15 per cent.

Other Symptoms.—Anorexia (4 per cent), wind (4 per cent), borborygmi (3 per cent), nausea (3 per cent), urgency (2 per cent): distension, breathlessness, and urinary difficulty were other complaints.

Acute Obstruction.—3·5 per cent of the patients with carcinoma of the rectum and rectosigmoid were admitted in acute obstruction.

Duration of Symptoms.—The average duration of symptoms was 5·5 months.

Mistakes and Errors in Diagnosis.—Few mistakes in the diagnosis of rectal cancer occurred when the patient reached hospital. In the great majority the growth was felt on rectal examination or seen on sigmoidoscopy, and the occasional errors were almost invariably due to the omission or delay in sigmoidoscopy when the growth had not been reached with the finger and reliance had been made on a negative barium enema. This is not an efficient investigation for the upper part of the rectum.

Unfortunately frequent mistakes and delays occurred before the patient reached hospital, and the most common was the diagnosis of piles, frequently without a rectal examination, and treatment by liquid paraffin, ointment, or suppositories. It is not easy to estimate the number of patients who are referred to hospital for a rectal complaint without a previous rectal examination, but it may be as high as 20 per cent. An early rectal examination would probably do more than anything else to improve the present results in the treatment of rectal cancer and if medical education has failed to make this a routine, it is possible that legal action may be more effective in the future. The following case may illustrate the dangers :—

A lady of 58 had been for some years on very friendly terms with her practitioner. For three years she had suffered from rectal bleeding and had frequently spoken to her doctor about it. He told her that it was due to piles and prescribed for the condition but did not examine the rectum. Unfortunately, after a quarrel, their friendship broke up. She sought the advice of another doctor, who did examine the rectum, and within a fortnight she had had a combined excision and was left with a permanent colostomy. She threatened to bring an action against her previous practitioner, and was with the greatest difficulty dissuaded from this course.

A COMPARISON OF SYMPTOMS

Table VII compares the frequency of the main symptoms with growths in different sites of the large bowel. Pain, vomiting, faintness, or lassitude are common in the right colon ; less common in the left. Complaint of bowel change and bleeding rise in frequency from the right colon to the rectum. Acute obstruction and peritonitis are most common with sigmoid growths. The passage of mucus is noted occasionally with carcinoma of the sigmoid : it is common with carcinoma of the rectum and was not mentioned with growths in other sites. A palpable mass was most commonly present with carcinoma of the right colon.

In this lecture I have tried to put before you the clinical picture of this disease. We have other methods to confirm or refute the diagnosis, but it is on the clinical signs that the first diagnosis, and so much of the future, depends. You will have seen that it is easy to make mistakes—a few can only be called negligent, some are due to carelessness, and the majority to errors in judgement and the false trails led by incomplete investigation. Many could have been avoided. " Experience teaches slowly and at the cost of mistakes " (Froude), but in the end it might perhaps be quicker and less costly if complaint in the elderly led to examination and investigation that was early, routine, and complete. Some sneer at the ' blunderbuss ' method of full investigation, but in surveying these cases it has seemed to me that it has often been the selection of one particular investigation, and the false assurance or wrong diagnosis resulting from it, that has caused the tragedy. We are to think of malignant disease of the bowel first when we hear of any patient over fifty complaining of abdominal discomfort that is not quite clearly gastric, and we must continue to think of it until it is excluded by repeated and careful physical examination, sigmoidoscopy, and radiological investigation that must include a barium enema.

It was Rochefoucauld who said : " In the misfortunes of our best friends we find something which is not displeasing to us ", and it is quite true that it is always interesting to relate the mistakes of others ! But whether we work in hospital or in practice we are all concerned in this.

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POLYOSTOTIC FIBROUS DYSPLASIA WITH CARCINOMA OF THE ŒSOPHAGUS

BY J. W. DICKSON AND W. W. RICHARDSON

FROM THE DEPARTMENT OF ORTHOPÆDICS AND THE BLAND-SUTTON INSTITUTE OF PATHOLOGY, MIDDLESEX HOSPITAL, LONDON, W.1.

THE case reported here is of interest in providing a further post-mortem account of polyostotic fibrous dysplasia, a condition in which detailed examination of all affected tissues is seldom possible. It emphasizes the occasional silent nature of œsophageal carcinoma, and shows osseous metastasis only to those bones already grossly affected by the dysplasia.

CASE REPORT

CLINICAL HISTORY.—The patient, a male, then aged 31, was first seen at St. Mary's Hospital in May, 1937, having twisted his ankle. Radiographs showed a cystic condition affecting the left tibia. A biopsy was reported as showing fibrocystic disease (neither the original radiographs nor the biopsy slides can now be traced). In 1939, radium needles were inserted. The patient stated that in 1941 the bone became infected, and an above knee

FIG. 1.—Pathological fracture through an area of fibrous dysplasia in proximal half of left humerus, June 12, 1952.

FIG. 2.—Left humerus on Aug. 19, 1954 for comparison with *Fig.* 1 after metastatic deposits had appeared.

amputation was performed. From then until 1952 he was well and continued at work.

In 1952 he sustained a fracture of the upper end of the left humerus (*Fig.* 1), and a radiological skeletal survey showed extensive involvement by fibrous dysplasia of the left humerus, lower end of the right fibula and sacrum. The fracture healed well.

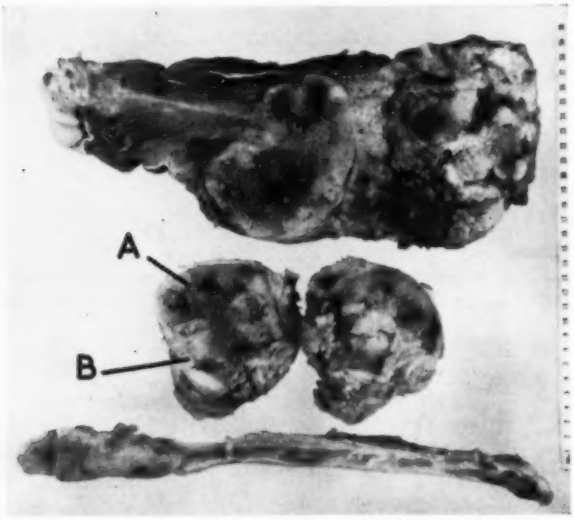

FIG. 3.—Left humerus, bisected sacrum, and right fibula. The humerus shows gross destruction by tumour. The anterior part of the sacrum A shows fibrous dysplasia and one small cyst; the posterior part B is occupied by tumour. The lower end of the fibula shows fibrous dysplasia and areas of carcinoma.

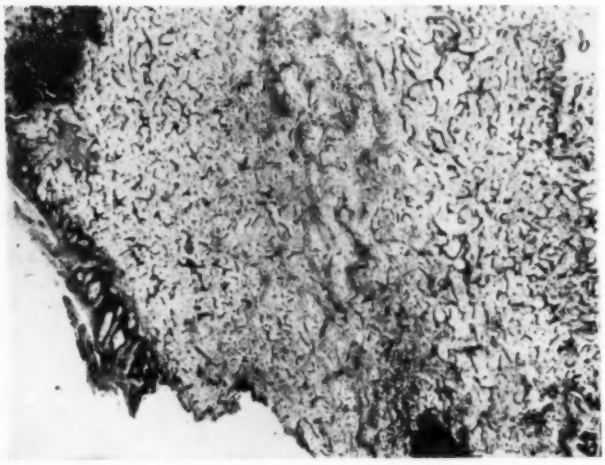

FIG. 5.—Section from lower end of right fibula showing fibrous dysplasia and invasion by carcinoma. (× 3.)

On Aug. 13, 1954 he complained of right sciatica of three months' duration. The upper end of the left humerus was noted to have increased in size (*Fig.* 2). No other symptoms were present, and there was no history suggesting alimentary disease. By Aug. 26 his condition had rapidly deteriorated, right sciatic pain was constant, and the left upper arm was occupied by an intensely painful, almost fungating tumour.

Biopsy of the upper humerus on Sept. 2 showed destruction of bone by a highly undifferentiated carcinoma.

INVESTIGATIONS.—

Hæmoglobin	13·7 g./100 ml.
Blood-urea	29 mg./100 ml. (74 hr. before death)
Alkaline phosphatase	57 K–A units/100 ml.
Acid phosphatase	2·65 K–A units/100 ml.
Serum calcium	10·4 mg./100 ml.

Patient died on Sept. 8.

POST-MORTEM FINDINGS.—The body was that of an emaciated middle-aged man; left mid-thigh amputation. Proximal two-thirds of left arm was grossly swollen and

FIG. 4.—Post-mortem radiograph of right fibula showing fibrous dysplasia and metastatic carcinoma.

there was a recent biopsy scar in deltoid region. Lower third of right fibula was irregularly expanded. The skin over the left humerus and right fibula was deeply pigmented.

In the œsophagus about 1 in. proximal to the cardiac orifice there was a large, sloughing, carcinomatous ulcer about 3 in. in diameter which had encircled the œsophageal wall without causing stenosis. Surrounding the tumour were many enlarged lymph-nodes, the largest about 1½ in. in diameter, occupied by firm white tumour material. These nodes extended to the middle of the thorax rostrally, and to the level of the cœliac axis caudally, where there was a matted clump about 4 in. × 3 in. × 3 in. in size. The stomach was normal.

The liver weighed 128 oz. (3650 g.) and contained numerous white nodules up to 3 in. in diameter; those on the surface were umbilicated, and hæmorrhage had occurred centrally into many of them.

In spite of a careful search only one parathyroid gland was found; this was ¼ in. (0·6 cm.) in length.

The left adrenal contained a metastatic tumour ¾ in. (1·8 cm.) in diameter. The thyroid was normal macroscopically.

The left humerus, sacrum, and right fibula showed enlargement and invasion by firm white tumour with hæmorrhagic areas, particularly gross in the upper end

of the humerus. The anterior surface of the sacrum, which was greatly expanded, and the proximal part of the lesion in the right fibula were macroscopically free from tumour (*Fig.* 3). In these regions the bone could be cut with a knife; on section the cortex was thin and the medulla was composed of a resilient greyish tissue containing numerous bony spicules. A cystic area 1·5 cm. in diameter filled with pink gelatinous material was present in the sacrum; this was the only cyst discovered.

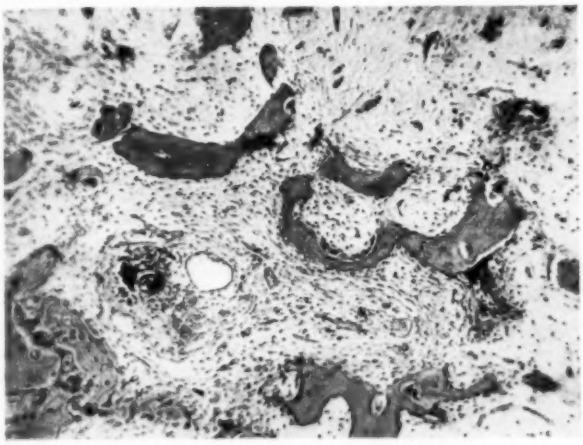

FIG. 6.—Lower end of fibula. (× 75.)

HISTOLOGY.—

Œsophagus.—The tumour in the lower third was an undifferentiated carcinoma showing much pleomorphism, many mitoses, and large areas of necrosis.

Metastases in the liver, abdominal and lower thoracic lymph-nodes, adrenal, and bones, were similar in appearance to the œsophageal tumour.

Thyroid.—Normal glandular pattern but the stroma showed early invasion by metastatic carcinoma.

Parathyroid.—Showed an increase in fibrous tissue stroma; the cells were almost entirely chief cells, with no evidence of hyperactivity.

Bones.—Unfortunately the invasion by carcinoma obscured a greater part of the dysplasia in the humerus, but the anterior part of the sacrum and parts of the fibula were relatively free of tumour and showed a thinned irregular cortex enclosing a medulla composed of loose fibrous tissue containing numerous poorly-formed bone trabeculæ (*Figs.* 5, 6). In areas there were prominent blood-vessels formed only by a single layer of endothelium; some of these in the sacrum contained tumour emboli (*Fig.* 6). Osteoclastic activity was slight or absent in most sections apart from those from the fibula which showed moderate activity in certain regions, more especially those related to invasion by carcinoma. Cysts —apart from the solitary degenerative one in the sacrum— did not occur, nor were cartilaginous areas present. Subperiosteal bone formation was prominent in most sections. This is not a feature of most reported cases of polyostotic fibrous dysplasia and we can only assume that invasion of the skeleton by carcinoma has provided this stimulus to osteogenesis, producing an appearance not unlike that of hypertrophic pulmonary osteo-arthropathy.

COMMENTS

On admission in 1954 it was first thought that malignant changes had occurred in an area of fibrous dysplasia (Coley and Stewart, 1945; Jaffe, 1946; Sutro, 1951). The œsophageal carcinoma was silent.

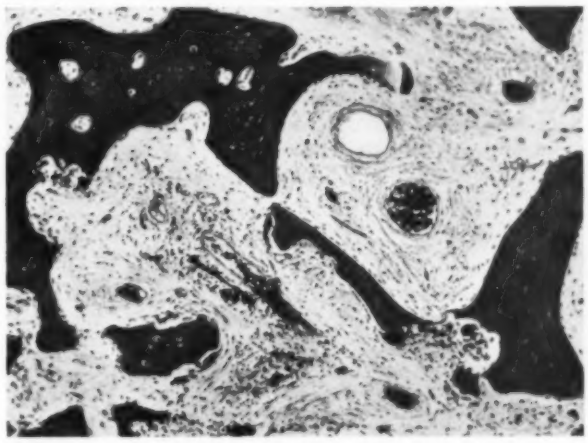

FIG. 7.—Sacrum showing tumour emboli in thin-walled blood-vessels. (× 75.)

Although metastasis had occurred to regional lymph-nodes, liver, one adrenal, and the thyroid, the only bones grossly involved were dysplastic. Excellent accounts of polyostotic fibrous dysplasia have been published by Lichtenstein (1938), Uehlinger (1940), Lichtenstein and Jaffe (1942), Falconer, Cope, and Robb-Smith (1942), Dockerty, Ghormley, Kennedy, and Pugh (1945), and Russell and Chandler (1950).

We wish to thank Mr. Philip Wiles and Professor R. W. Scarff for permission to publish this case, and Dr. A. D. Thomson for help with the histology.

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THE OUTLOOK AFTER MASSIVE RESECTION OF SMALL INTESTINE, WITH A REPORT OF TWO CASES

By H. S. TRAFFORD

FROM THE NORTH STAFFORDSHIRE ROYAL INFIRMARY, STOKE-ON-TRENT

THE problem of extensive resection of small bowel has become of increasing interest of late because it is now quite obvious that with suitable adjustment of a patient's blood chemistry, resection of 90 per cent of the ileum and jejunum is under certain circumstances quite compatible with life, and, secondly, recent attention has been drawn to the resection of lengths of jejunum in the treatment of obesity.

CASE REPORTS

Case 1.—W. G., aged 25, was first seen in April, 1949, when he was admitted as an acute emergency with what was thought to be acute appendicitis. At operation fairly

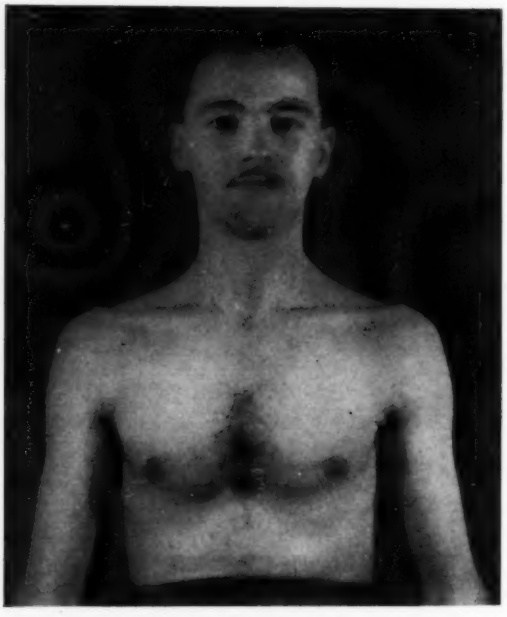

FIG. 8.—*Case* 1. Man of 25 years of age, 3 years after massive intestinal resection.

extensive regional ileitis was found in the acute phase, and appendicectomy only was performed. In May, 1949, he was re-admitted with obstructive symptoms, and at operation an ileotransverse anastomosis was performed, using ileum well above the last area of bowel affected by the ileitis. He recovered, and remained well until December, 1951, when he was re-admitted with recurrence of his pain and diarrhœa.

He was built up with a view to laparotomy and, if possible, resection. At operation practically the whole of his ileum and jejunum was involved by Crohn's disease, and was matted together. It was found necessary to resect all but 2½ ft. of jejunum, and this resection had to be continued up to his old ileotransverse anastomosis, and the stump of jejunum anastomosed side to end with the middle of the transverse colon.

He made quite a good recovery, and when discharged three weeks later he was only having 4 to 5 bowel movements per day and was gaining weight. He was discharged on a high protein and carbohydrate and a low fat diet.

He remained well until June, 1952, when he was re-admitted to the medical wards with a deficiency

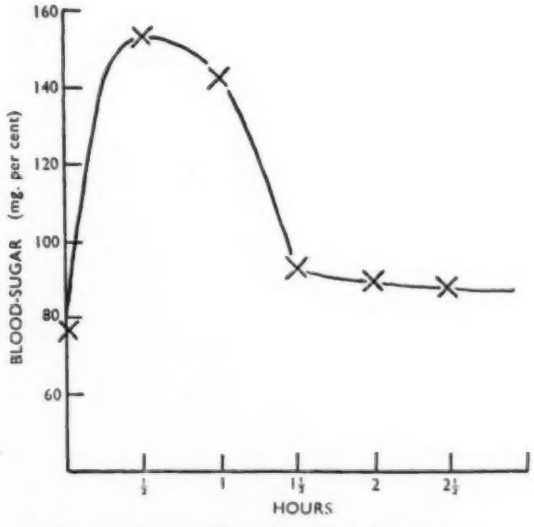

FIG. 9.—*Case* 1. Normal glucose tolerance curve.

FIG. 10.—*Case* 1. Barium meal showing appearance of remaining 2½ feet of small bowel with ileo-transverse anastomosis.

anæmia and a hæmoglobin of only 36 per cent. He had a blood transfusion and iron therapy, and after several weeks his hæmoglobin rose to 90 per cent. He was re-admitted for similar treatment in December, 1952, and has continued on iron ever since. His weight at this time was 10 st. 6 lb.

Present State.—A fit healthy young man (*Fig.* 8) of weight 11 st. 2 lb. His bowels are open 4 times daily, and he has a semi-solid stool. He is on a maintenance dose of iron and folic acid, and he is doing a moderately heavy job as a packer. Apart from avoiding excess fats he does not bother very much with his diet. *Table I* shows the patient's blood chemistry to be well within normal limits. The raised serum potassium is due to serum hæmolysis. *Table II* shows that he has a normal hæmoglobin and prothrombin index. *Table III* shows as would be expected a high total fat content in the fæces, and this patient is not splitting his fat as well as he should be. *Fig.* 9 shows a normal glucose tolerance curve, and the rapid rise to a maximum suggests that absorption is occurring mainly in the stomach and small bowel. *Fig.* 10 shows a recent barium meal, which demonstrates the small amount of small bowel remaining and visualizes the ileotransverse anastomosis. There has been slight hypertrophy of the remaining small bowel and some dilatation and alteration of the mucosal pattern of the duodenum.

Table I.—Blood Chemistry

Serum	*Case 1*	*Case 2*	*Normal Range*
Urea	15 mg. per cent	30 mg. per cent	15–40
Sodium	316 mg. per cent	339 mg. per cent	310–330
Potassium	22·5 mg. per cent	15·2 mg. per cent	16–21
Chlorides (as NaCl)	620 mg. per cent	620 mg. per cent	560–620
CO_2 combining power	62 c.c. CO_2 per 100 c.c.	58 c.c. CO_2 per 100 c.c.	50–70
Plasma protein	6·8 g. per cent (Alb./glob. ratio 1·7)	6·9 g. per cent (Alb./glob. ratio 1·7)	6·4–8·5 (Alb./glob. ratio 1·7)

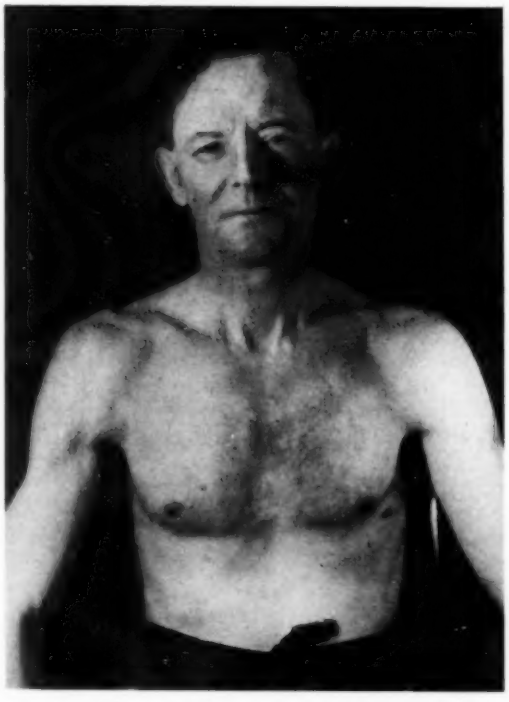

Fig. 11.—*Case* 2. Man of 51 years of age, 3½ years years after massive small gut resection.

Table II.—Hæmoglobin and Prothrombin Index

Serum	*Case 1*	*Case 2*
Hæmoglobin per cent	99 per cent	66 per cent
Prothrombin index	100 per cent	100 per cent

Case 2.—H. B., aged 51, was first admitted to hospital in 1947 with regional ileitis, and about 4 ft. of affected bowel was resected with ileo-ileal anastomosis. He remained well until 1950, when his diarrhœa returned, and at a further laparotomy the disease was found to have recurred, and it was necessary to remove a further 5 ft. of ileum. He was next seen in November, 1951, when he was admitted to hospital as an emergency in a very shocked state with symptoms of acute intestinal obstruction. At operation the abdomen was found to be full of gangrenous small bowel due to an omental band encircling its mesentery. The only remaining viable small bowel was the first 15–18 in. of jejunum. After resection of the gangrenous portion the jejunum was implanted into the cæcum by side-to-side anastomosis. There was just enough jejunum to stretch to the cæcum without undue tension. After a stormy first few days he recovered well from this operation, and was discharged 3½ weeks later on a high protein and carbohydrate and low fat diet. He was having 6 to 7 stools a day, but these were semi-solid.

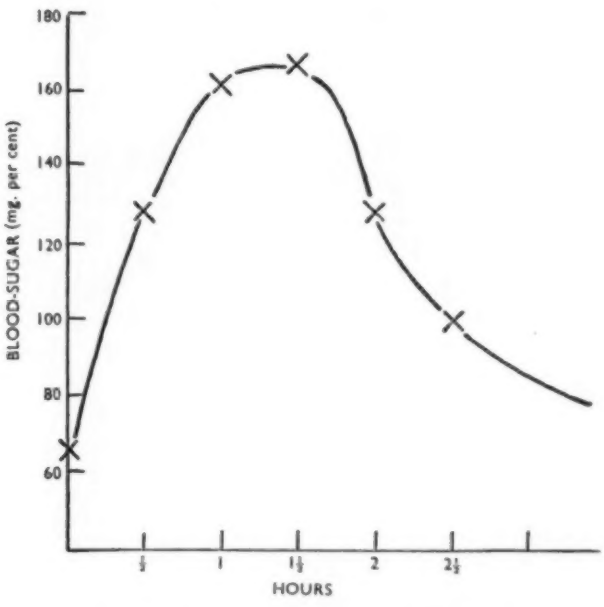

Fig. 12.—*Case* 2. Normal glucose tolerance curve.

Table III.—Fat Content of Fæces

Fæces	*Case 1*	*Case 2*
Total fat	58 per cent	54 per cent
Split	66 per cent	89 per cent
Unsplit	34 per cent	11 per cent

He was next seen as an out-patient in March, 1952, in a very poor state, with gross muscular weakness and a blood-pressure of only 90/50. His weight was now only 6 st. He was admitted immediately, and put on intensive carbohydrate and protein therapy intravenously and given fairly large doses of potassium, both orally and in the drip, as his serum potassium was only 9 mg. per cent. He gradually improved, and was discharged 7 weeks later,

when he was 7 st. 2 lb. in weight, and his serum potassium was 14·5 mg. per cent. His doctor was instructed to give him potassium chloride, gr. 5, three times daily at home. He steadily gained ground, and was seen

FIG. 13.—*Case* 2. Barium meal showing duodenum and small loop of jejunum with ileo-cæcal anastomosis.

regularly as an out-patient until October, 1952, when his weight had increased to 10 st. and he was only having 3 to 4 motions per day.

Present State.—A fit healthy man for his age (*Fig.* 11) of weight 10 st. 6 lb. His bowel action is his only complaint, as some days he has 7 to 8 bowel actions, but on a good day only 2. The stool is always semi-solid. He does not trouble much with his diet except that he avoids too much fruit, as this upsets his bowel habit. He does a fairly heavy day's work as a farmer on his own farm. *Table I* shows this man's blood chemistry to be within normal limits except his serum potassium, which has always been on the low side but is now much higher than it was shortly after operation. *Table II* shows a normal prothrombin index, but a rather low hæmoglobin per cent. *Table III* shows, as in *Case* 1, rather a high total fat content of the fæces, but in contrast to *Case* 1 the proportion of split to unsplit fat is within normal limits. *Fig.* 12 shows rather a large type of glucose tolerance curve in this case, suggesting possibly that most of the glucose absorption occurs only when it reaches the colon. *Fig.* 13 shows a striking barium meal in this case, with only a small amount of small bowel visible, and the ileo-cæcal anastomosis. There is obvious dilatation and hypertrophy of the mucous membrane and lumen of the duodenum.

REVIEW OF THE LITERATURE

Senn in 1888 was one of the first writers to discuss the problem of massive intestinal resection in any detail, and he was of the opinion that one third or up to 6½ ft. of small bowel could be removed without serious nutritional disturbance to the individual. Haymond, in reviewing the literature in 1935, collected 257 reported cases in which 6 ft. or more of small bowel had been removed for various reasons. The overall operative mortality was 33·5 per cent, which he felt was not a true figure, as unsuccessful cases tend not to be reported in the literature; 36·7 per cent of the survivors were reported to have done well. Eighty-six of the cases had had 47·2 per cent of small bowel removed on the average with satisfactory results. Twenty-one cases had a fair result with removal of 55·8 per cent of bowel, and 15 cases with an average of only 52·9 per cent removed had a poor result. He concluded that 50 per cent removal of small intestine constitutes the upper limit of safety.

Some successful cases reported more recently have only been left with 3½ ft. or less of jejunum. A patient studied by West (1938) was troubled by recurrent tetany due to a low blood-calcium. Washburn (1929) reports a case recently in which the patient is alive and well 22 years after removal of two-thirds of the small bowel. Weckesser, Chinn, Scott, and Price (1949) report 3 cases of extensive resection in which 2 cases had 88 per cent of the bowel removed, but both died of inanition nine months later. The third case had severe digestive disturbances following removal of only 5½ ft. (25 per cent) of the ileum and the colon for mesenteric thrombosis.

DISCUSSION

The two cases under discussion had 89 per cent and 93 per cent of their small bowel removed respectively, the former case also having his right colon resected in addition. The younger man (*Case* 1) was troubled initially by an iron deficiency anæmia, the older man (*Case* 2) suffered from potassium depletion, but both have to a large extent corrected themselves and are leading normal lives. Both are troubled by loose frequent motions, but have learned what articles of diet make this worse. Both have gained weight since their operations, contrary to the experience of other authors. It is suggested that after massive intestinal resection the duodenum and colon take on some of the absorptive functions of the small intestine, and that the remaining gut may dilate and hypertrophy to some degree. Preservation of as much colon as possible in these cases appears desirable, and cases in which resection has been in stages appear to do best.

SUMMARY

Two cases of resection of 89 per cent and 93 per cent of the total small bowel are recorded. Both are alive and healthy 3½ years afterwards. Some of the main literature on the subject is reviewed, and a few theories put forward on the possible compensatory phenomena occurring in the body as a result of this extensive resection. If the patient can be tided over the first post-operative year then the chances of survival appear good. *Case* 2 is submitted as being the most extensive resection of small gut on record in which the patient has survived for such a long period. The main complications following massive intestinal resection appear to be diarrhœa, loss of weight, anæmia, potassium deficiency, and tetany. If only a small amount of jejunum remains the outlook is not hopeless, but resection of small gut for obesity would appear to be a very uncertain measure.

My thanks are due to Mr. J. S. Ramage for permission to publish these case histories, and for

helpful advice in the preparation of this paper. I am also indebted to Dr. A. J. McCall and Dr. E. C. Butterworth of our Pathology Department for the blood chemistry, and to Dr. C. G. Edwards of the Radiological Department for the X-ray investigations. I also appreciate the help given by the Department of Clinical Photography and for their assistance with the photographs and photographic prints of the X-rays.

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BELOW-KNEE AMPUTATION IN ARTERIOSCLEROTIC GANGRENE

By R. R. KENDRICK

SENIOR SURGICAL REGISTRAR, GRAVESEND AND NORTH KENT HOSPITAL

For generations above-knee amputation for arteriosclerotic gangrene has been the site of necessity rather than of election. The frequency of infection, with its grave danger to life and limb, discouraged attempts to amputate at a lower level. In 1939 Homans was voicing contemporary surgical opinion concerning arteriosclerosis of the lower limb when he wrote " Amputations below the knee can almost never be expected to offer a healthy stump ". Since then, however, many advances in treatment have been made, especially the introduction of antibiotics, and it is the purpose of this paper to demonstrate that to-day Homan's contention is no longer applicable.

In cases of ischæmic gangrene which warrant major amputation, there still appears to be a widespread feeling that one below the knee is bound to fail. Consequently many surgeons proceed at once to an above-knee amputation, when a local amputation has failed or is not indicated. Increasing experience is, however, convincing us that amputation through the mid-calf can be relied upon to heal soundly in the large majority of these cases. This is of considerable importance because a below-knee amputation has marked advantages over one above the knee at any age, but especially in the elderly. With relatively few exceptions, ischæmic gangrene occurs in association with arteriosclerosis and so these patients are frequently of advanced age.

THE ADVANTAGES OF BELOW-KNEE AMPUTATION

Amputation below the knee permits better balance either with crutches or with a prosthesis; this difference in the elderly patient may mean that he is ambulatory, with all that that implies.

Walking is achieved following a below-knee amputation with greater facility and far less physical effort due to the longer and more efficient lever present. Silbert and Haimovici (1954) found in a group of mid-thigh amputations for obliterative arterial disease that only half of the men and almost none of the women ever accustomed themselves to the use of an artificial limb; and yet we have seen a man aged 84 walking without a stick and almost without a limp less than 3 months following a below-knee amputation.

In contrast to one above the knee the below-knee stump is rarely associated with stump or phantom limb pains. Also, of course, the desirable normal movements of the knee-joint are retained.

The patient with a below-knee amputation has greater stability and freedom of movement when seated in a chair or even lying in bed, and it must be remembered that not infrequently both legs will eventually require amputation. Paradoxically it has been found easier to rehabilitate a double above-knee amputee than one in whom one amputation is above, and the other below the knee (McKenzie, 1953), because in the former case initial walking training may be given on short pylons, on which the patient is as near to the ground as possible, and effort is minimized. Thus at least some measure of independence is gained even although the patient may never be able to manage full length articulated prostheses.

Table I.—ANALYSIS OF 59 MAJOR AMPUTATIONS FOR VASCULAR DISEASE IN 48 PATIENTS

	ABOVE-KNEE AMPUTATION	BELOW-KNEE AMPUTATION
Male	6 (2)	42 in 33 patients (4)
Female	2 (1)	9 in 7 patients (3)

The figures in parentheses refer to patients with diabetes mellitus.

For several years it has been our endeavour to employ a below-knee amputation in preference to one above the knee whenever possible. To determine the results of this policy a study has been made of a consecutive series of cases, consisting of all the major leg amputations performed for peripheral vascular disease during the past 6 years at the Gravesend and North Kent Hospital and, more recently, in the Peripheral Vascular Unit at Joyce Green Hospital, Dartford.

Conservative treatment and local amputation (through the proximal phalanx, or metatarsal head or neck of one or more toes) was attempted and persisted in whenever feasible, and major amputation was performed only when these measures had failed or held no prospect of success.

Transmetatarsal amputation has been described by Furste and Hermann (1948), McKittrick, McKittrick, and Risley (1949), and Haimovici (1955). They have obtained healing by first intention in about one-third of their cases, and healing with some

delay in another third. Most of their amputations were performed on diabetic patients. We have been less successful in amputations at this level in patients with arteriosclerotic gangrene, and our preference has usually been for amputation through the calf. Certainly no amputation at any intervening level offers promise of satisfactory rehabilitation in ischæmic gangrene.

Table II.—Distribution in Age Groups

Age	Arteriosclerosis		Thrombo-angiitis Obliterans (All Males)
	Male	Female	
20–29			1
30–39			2
40–49			1
50–59	8	1	
60–69	11	1	
70–79	15	4	
80–89	1	3	

Table II suggests that gangrene is uncommon in women under the age of 70. In fact in 19 cases of gangrene in women who have come under our care only 2 were less than 69 years old. There were 59 amputations in 48 patients. In the same period three patients, all females, were inoperable. Each would have required an above-knee amputation had she been fit enough.

In 8 cases above-knee amputation was performed. Once because gangrene of the foot was associated with severe painful osteo-arthritis of the knee-joint and, in the remaining 7 cases, it was inevitable because gangrene extended far up the leg.

There were 51 below-knee amputations in 40 patients. Forty-three were due to arteriosclerosis complicated in 7 instances by diabetes mellitus. These last patients were all suffering from peripheral arteriosclerosis in addition to their diabetes. No below-knee amputation was performed in a diabetic patient for neuropathic or infective gangrene unassociated with advanced peripheral arteriosclerosis. Five amputations were due to thrombo-angiitis obliterans. These cases are included because apart from belonging to a younger age group, the essential problem is similar to that of the arteriosclerotic limb, and indeed both pathological processes may be present at the same time. Frost-bite precipitated gangrene involving the whole of both feet in an old tramp following a night spent in the open in mid-winter. A bilateral below-knee amputation was required. The remaining amputation was probably due to an arterial embolus.

Gangrene was the indication for amputation in every case except one. It was felt that lumbar sympathectomy had prevented the onset of gangrene in this patient. He had marked cold rubor of both feet and nothing was found to relieve his constant severe pain. He finally had both legs amputated. In other similar circumstances we have found the anticoagulant drugs to be the most effective agents in relieving such pain.

LUMBAR SYMPATHECTOMY

Many patients are seen for the first time only when gangrene is well established and a major amputation is inevitable. Sympathectomy was not performed either preceding or coincident with the amputation procedure in these cases. On the other hand if there was a possibility of eradication of the gangrene locally, lumbar sympathectomy was undertaken in an attempt to improve the blood-supply to the foot. Experience has shown that the sympathectomy should be delayed until a reasonable line of demarcation is present; this indicates the establishment of an effective collateral circulation.

Lumbar sympathectomy preceded below-knee amputation on 20 occasions. Little difference in the rate and soundness of healing of the stump was observed as a result.

A strong case exists for performing a lumbar sympathectomy on the ' sound ' side if any signs or symptoms of vascular insufficiency are present and if the general condition of the patient warrants such a procedure. Bilateral gangrene is by no means rare in peripheral arteriosclerosis. There is little doubt that a lumbar sympathectomy performed in time can often prevent the onset of gangrene.

An unexpectedly high proportion of patients in this series, almost one in five, have had bilateral amputations. The number of cases is too small to draw any conclusions, but it is interesting to note that McKittrick (1940) analysing 972 cases of diabetic gangrene found an incidence of 40 per cent of bilateral gangrene and 17 per cent of bilateral amputations.

Table III.—Pathological Condition for which Amputation was Performed

Pathology	Above-knee Amputation	Below-knee Amputation
Arteriosclerosis	8	43 (Bilateral amputation in 9 patients)
Thrombo-angiitis obliterans		5 (Bilateral amputation in 1 patient)
Frost-bite		2 (Bilateral amputation)
Embolic gangrene		1

The importance of taking every care to protect the unaffected foot from trauma of any kind cannot be exaggerated. It must be explained to the patient himself and understood by all those in attendance on him. Following amputation of one foot, the remaining heel, which is often already susceptible to injury by pressure, receives twice the normal amount of pressure every time the patient moves himself in bed. Various types of complicated slings have been devised to keep the heel from resting on the bed, but a satisfactory method is to surround the foot with cotton-wool, which is loosely bandaged in place.

CONTRA-INDICATIONS TO BELOW-KNEE AMPUTATION

It is simpler to formulate the contra-indications than the indications for a below-knee amputation.

The contra-indications are few, viz. :—

1. Marked flexion contracture of the knee. Many patients with severe rest pain tend to sit up in bed in a characteristic attitude with the knee acutely flexed; contracture occurs rapidly if amputation is unduly delayed. If of short duration, the

contracture may be easily overcome by active exercises following amputation, but often it is permanent and then fitting a prosthesis may be impossible. Actually the socket can be made so that it accommodates a stump with about 30° of flexion.

2. Trophic changes of the skin or obvious infection extending as far proximally as the skin-flaps will require above-knee amputation.

3. Recent sudden occlusion of the iliac or femoral arteries will usually require an above-knee amputation, unless the formation of a collateral circulation has already been in part established. It may be impossible to determine accurately the fate of the limb at once, and in such circumstances expectant treatment is indicated with anticoagulants, reflex vasodilatation, and judicious temperature control of the limb.

The indications for below-knee amputation may be stated as follows :—

1. When conservative amputation (through the proximal phalanx or metatarsal head or neck of one or more toes) has failed, and gangrene is spreading. This was the indication for below-knee amputation in 14 cases in this series.

2. Gangrene of one or more toes associated with extensive gangrene of the heel or dorsum of the foot.

3. Gangrene of a toe and often cold rubor of the adjacent area of the forefoot associated with severe rest pain in the foot extending towards the ankle.

4. Occasionally in the grossly ischæmic foot associated with severe and intractable resting pain in the absence of gangrene.

Cutaneous anæsthesia is an adverse factor in ischæmic gangrene, and might indicate the need for a below-knee amputation, when a more conservative course would otherwise have been taken.

Rapidly spreading infection which cannot be controlled by antibiotics is rarely seen to-day. It calls for urgent amputation. If the infection is confined to the foot a below-knee amputation is indicated, but if lymphangitis or cellulitis is extending up the tissue planes of the leg amputation above the knee must be performed. A guillotine amputation was frequently practised for this type of infection, but it rarely results in a suitable stump for a prosthesis, and before one can be fitted an amputation at a higher level must be performed. The better drainage a guillotine amputation provides does not compensate for the disadvantage of two operations in an old patient.

It has often been stated that absence of a popliteal pulse is a contra-indication to amputation below the knee, but in this series it was palpable in only 5 cases. It is sometimes difficult to be certain whether a popliteal pulse is present or not. Oscillometry is then of great value in confirmation. However, the oscillometer cannot be relied on to determine the site at which amputation should be performed. It is a most useful instrument in indicating main vessel block, but is less accurate in reflecting the effectiveness of the collateral circulation. An appreciable swing below the knee provides strong evidence that a below-knee amputation will succeed, but absence of swing in a sensitive oscillometer does not necessarily mean that a below-knee amputation will fail. On five occasions oscillometric readings were absent both above and below the knee, and as would be expected this was an unfavourable finding; one of these cases failed and two healed only after some delay, but two cases healed by primary union.

Shumacker and Moore (1951) state that the best test of adequate blood-supply is a trial incision in the leg to show the gross vascularity. In our experience this test, if used, should be most generously interpreted. On several occasions the skin-flaps have virtually not bled a drop and yet even to our surprise, healing by first intention has taken place.

In general a below-knee amputation may be attempted however poor the circulation of the leg may appear, if the area of skin of the flaps is healthy and rapidly extending gangrene, which indicates spreading thrombosis, is not present below. Even if it fails it is not a tragedy, but usually it will succeed.

If for some reason it will be impossible to use a prosthesis some authorities advise an above-knee amputation as being the most rapid and certain method to obtain healing. This is possibly true but against this must be weighed the psychological and mechanical advantages of a below-knee stump which have already been enumerated.

Results

Healing was obtained in the below-knee amputations as follows :—

First intention healing	32 (63 per cent)
Delayed healing (6–18 weeks)	11
Amputation stump refashioned	3
Failed (above-knee amputation required)	2
Died before healing was complete	3

Delayed healing may be due to a narrow area of necrosis along the line of approximation of the wound. This often, although not always, results in a scar adherent to the underlying bone. This is naturally to be avoided if possible, but nevertheless it is usually painless and functions perfectly well in a prosthesis.

In 3 cases a triangular patch of gangrene appeared in the anterior flap overlying the tibial stump. Healing would have taken several months and in order to avoid this delay the stump was refashioned and the bone sectioned 2–3 cm. higher. Healing promptly followed.

Failure to heal completely occurred only twice in those patients who survived the operation; infection and gangrene of the wound supervened, the knee-joint became fixed in flexion, and subsequent re-amputation was performed above the knee.

There were 3 hospital deaths following below-knee amputation. A diabetic female aged 82 was extremely toxic on admission. Extensive spreading moist gangrene of the foot, secondary to a hot water bottle burn, was treated by amputation of two toes and by wide débridement and every effort was made to control her diabetes. This failed to limit the toxæmia or the spread of infection. Below-knee amputation was performed four days later, as soon as permission to amputate was obtained. She died within 24 hours. Undue delay in this case prejudiced a successful outcome.

A female, aged 85, had been bedridden for six years with an unreduced congenital dislocation of

the hip and advanced senility. She had extensive, apparently painful, gangrene of the foot and decubitus gangrene of the ankle and so a below-knee amputation was done. The stump was soundly healed in 14 days. She died 4 weeks later from a cerebral hæmorrhage, whilst awaiting transfer to a geriatric unit.

A woman, aged 87, was admitted with gangrene of one foot for which a below-knee amputation was performed. Almost immediately extensive gangrene developed in the remaining foot, which was amputated two months later. She developed cerebral thrombosis and died soon afterwards. At this time the original amputation was not quite healed.

Advanced age by itself appears to have no delaying effect at all on the rate or soundness of healing and, in this respect, as in many other branches of surgery, the general condition of the patient and the relative age of the tissues are far more important than the actual chronological age.

Two patients had marked angina of effort after walking more than a few paces. It was felt the extra exertion required following a mid-thigh amputation might have prevented walking at all.

No patient admitted to any phantom limb pains and there was no complaint of pain in the stump from the time healing was complete.

When the stump has healed it has remained healed without difficulty and there has been no incident of recurrent ulceration, but expert manufacture and, above all, fitting of the prosthesis is essential.

One case remained securely healed for 19 months and in this time the patient had used a prosthesis for more than a year with complete success. However, a few days following amputation of the contralateral limb for gangrene, the below-knee stump developed massive necrosis and an above-knee amputation was required. This would appear to be a quite exceptional occurrence. The operative procedure apparently precipitated an acute femoral thrombosis in the opposite leg.

ANÆSTHESIA

General anæsthesia is preferred for amputation. Ice anæsthesia was used on six occasions when a general anæsthetic was considered especially hazardous. For a below-knee amputation a tourniquet is applied just above the knee and the limb is surrounded with finely chipped ice from this level downwards for about 2½ hours.

Two of the hospital deaths in this series occurred following refrigeration anæsthesia but this is not surprising in view of the fact that they were already judged very poor risks.

Probably healing is slightly delayed by refrigeration, but it may be a price that is well worth paying in certain circumstances.

A complication associated with ice anæsthesia was seen in one patient. A slough of the whole thickness of the skin 12 × 7 cm. occurred over the patella and ligamentum patellæ, which must have been due to small vessel occlusion, because the actual amputation wound healed in about 14 days. The most likely cause of the slough was that the bandage was too tightly applied at the end of the operation. It is even more important to avoid undue pressure beneath the bandage following amputation with ice than it is after general anæsthesia. P. Jayes has kindly done a completely successful full thickness graft to the area of the skin loss.

Tourniquet and refrigeration to exclude a gangrenous and infected area is used in some centres to gain time to improve the general condition of an ill patient. A formal amputation is performed later at a higher level. We attempted it twice for this purpose. On one occasion the leg was successfully amputated just below the hip-joint a few days later. The other patient was moribund on admission and died within a few hours.

A below-knee amputation performed with ice anæsthesia is followed by such little shock or other disturbance that there would appear to be little advantage in postponing the amputation. It certainly simplifies the management of a severely ill diabetic patient.

TECHNIQUE OF THE AMPUTATION

It is not proposed to describe all the steps of the operation in detail, but to stress some points considered important. Smears are taken from any ulcerated area for culture and suitable antibiotics are administered before and after operation as a routine in all cases.

Tourniquet.—If the extremity is wasted and the blood-flow is minimal no tourniquet is used. Otherwise we prefer to empty the limb of blood as far as possible by elevating it for a short time and then applying a pneumatic cuff just above the knee. The cuff is released as soon as the limb is removed and the main vessels have been ligated. In theory a tourniquet is obviously undesirable, but this procedure seems perfectly harmless and renders loss of blood negligible.

Skin-flaps.—Anterior and posterior flaps are used. The posterior flap is made twice as long as the anterior, because gangrene in our experience has affected only the anterior flap.

If there is any tension at all healing will fail and so a generous length of flap is allowed. Skin is elastic and any slight redundancy rapidly disappears.

The skin-flaps are cut so that the sum of their length is equal to half the circumference of the limb at the line of section through the tibia. A simple method to define the skin-flaps is as follows; the level chosen for section of the tibia is marked with ink, and the circumference at this point is measured in a moment by passing a piece of thread around the limb. The thread is then folded on itself and measured on a ruler; two-thirds is used to mark out the length of the posterior flap and one third that of the anterior.

The flaps consist of skin and deep fascia and the periosteum overlying the subcutaneous surface of the tibia. The muscles are divided at the line of section of the tibia. The average length of the tibial stump was 11·5 cm. in this series of ischæmic cases, which is slightly shorter than the 15 cm. recommended for the standard below-knee amputation.

The anterior border of the tibia is bevelled with a very oblique saw cut and the tibia is sawn through at right angles to its long axis. Any sharp angles which may remain are rounded off with a file. The fibula is stripped clean with a rugine and is divided

with a Gigli saw at a level 2·5 cm. higher than the tibia.

Hæmostasis is secured with 00 plain catgut for large vessels and with diathermy to small bleeding points. A stronger material may be required to crush a large calcified artery.

A few interrupted fine catgut sutures are used to unite the deep fascia. The flaps are then approximated as gently as possible with No. 100 thread on fine sharp needles, using some vertical mattress sutures, the deeper bite of which pick up the edges of the fascia. It is best to avoid using dissecting forceps on the skin edges. The minimal number of stitches is used consistent with exact apposition of the skin edges and care is taken not to strangulate the tissues contained within the stitches.

In about 20 per cent of cases the wound appears absolutely dry and no drain is inserted; otherwise drainage is preferred. In cases of doubt the presence or absence of bleeding from the tibial stump is a useful indication of the need for drainage. When required, a drainage-tube about 0·4 cm. in diameter is sutured in position through a stab incision, just proximal to each angle of the wound, so that the tube of one side almost meets that of the opposite side in the midline beneath the deep fascia. The tubes are left long so that they emerge through the crêpe bandages, which keep the wool and gauze dressings snugly but not tightly in place. The end of each tube is wrapped in a small antiseptic dressing and is aspirated four times per day. An adaptor is fitted at the end of each tube, into which an obturator is inserted to simplify aspiration, otherwise it is necessary to clamp one tube whilst the other is aspirated. Initially about 1–2 c.c. of blood-stained serum are obtained at each aspiration. When this amount diminishes to almost nothing, generally after 48 to 72 hours, the tubes are removed and the wound redressed.

It has often been said that a drainage-tube courts infection. This has no longer been tenable since antibiotics have been available, but a hæmatoma is still liable to be disastrous in a below-knee amputation.

The stump rests on a soft pillow, which counteracts any tendency to contracture of the knee-joint and prevents pressure on the vulnerable anterior flap by the underlying tibia.

In the absence of pyrexia or undue pain (which is due to a hæmatoma until proved otherwise) the dressings are not disturbed again until the twelfth day, when the sutures are removed if the wound appears healed. If healing is in any way doubtful some or all of the stitches are left in for a few more days.

Patients are kept in bed during this period of healing and are instructed in breathing and general exercises. If the few patients who could get about on crutches during this stage are allowed to do so, it appears to retard healing and cause increased pain in the stump. Also falls are not uncommon during this period and generally the stump bears the brunt.

A crêpe bandage is applied to the healed stump to hasten the inevitable shrinkage of the subcutaneous soft tissues, and to control any tendency to terminal œdema. Such œdema is common in a long below-knee stump, but is usually slight or absent in a short (10–12 cm.) stump. If the soft tissues are divided at the level of tibial section and the fibula is sectioned 2·5 cm. higher, a tapering stump is obtained which, especially in a thin subject, requires very little remodelling and is ready for fitting with a prosthesis almost as soon as healing of the wound is complete. Very great care must be taken to avoid applying the bandage too tightly. Necrosis due to pressure is easily produced especially if an elastic bandage is used with which it may be difficult to gauge the degree of compression.

SUMMARY

1. In peripheral vascular disease, and especially in arteriosclerotic gangrene, below-knee amputation offers very many advantages over above-knee amputation and can often be performed successfully.

2. In a consecutive series of amputations of the lower limb for obliterative arterial disease 51 were performed through the calf, of which 32 (63 per cent) healed by first intention. Three patients died. Healing failed in 2 cases and above-knee amputation was required. In addition, massive necrosis occurred in one stump, which had remained soundly healed for eighteen months.

3. Refrigeration anæsthesia is considered to be of value in a few patients in whom the operative risk is very great.

4. Some points in the technique of the amputation are described, and in particular the need for gentleness and accuracy in suturing the skin-flaps. Formation of a hæmatoma is a serious complication in these amputations and, unless the wound is completely dry, drainage is preferred.

5. In arteriosclerotic gangrene of the foot requiring major amputation, there are few contra-indications to below-knee amputation. This can nearly always be relied upon to heal rapidly and well, providing an excellent stump for a prosthesis and is much to be preferred to an above-knee amputation.

6. It is believed that successful primary healing of below-knee amputations in almost two-thirds of a series of patients whose popliteal pulses were absent is worth recording.

I wish to thank Mr. Sol. M. Cohen under whose care these patients were admitted for much helpful advice in the preparation of this paper.

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PERFORATION OF A CONGENITAL CYST OF THE COMMON BILE-DUCT

By R. E. B. TAGART
NEWMARKET GENERAL HOSPITAL

CONGENITAL idiopathic dilatation of the common bile-duct, or congenital choledochous cyst, has been fully described by Gross (1933, 1953), Walton (1939) and others. It is a rare condition, affecting females four times as commonly as males. Symptoms and signs very seldom become manifest before the age of six months, an important point in the clinical differentiation between this condition and congenital atresia of the bile-ducts. In a series analysed by Gross, 48 per cent of cases presented before the age of 20 years, 83 per cent before 30 years, the remaining 17 per cent being over 30 at the time of their first admission to hospital.

The main pathological feature is a striking enlargement of the whole or part of the common bile-duct. This enlargement is usually spherical but, in a few reported cases, it has been fusiform. The distension may involve the common bile-duct alone or it may include the junction of the cystic, hepatic, and common ducts. It is rare for the dilatation to extend so low that the pancreatic duct opens into the choledochal cyst. This localized dilatation of the common duct, with the gall-bladder very seldom distended, is in marked contrast to the generalized dilatation of the biliary tree which is secondary to organic obstruction.

The choledochous cyst may become very large, containing one to two litres. The cyst wall is usually about two to four millimetres thick and shows marked inflammatory reaction with absence of its lining epithelium. This inflammatory reaction has been known to cause complete obliteration of the outlet from the cyst. Other secondary changes are valve-like plications of the mucosa and narrowing of the common duct below the cyst.

There have been numerous suggestions as to the aetiology of this condition. Gross thinks it most likely that there is a congenital weakness of part of the wall of the common bile-duct and that this part stretches to form a ' cyst ' as a result of some relatively slight and intermittent obstruction lower down in the duct. He does not suggest what this obstruction may be. In the present case, the muscle-fibres in the lower part of the wall of the common bile-duct appeared to be very well developed (*Fig.* 18) and it is just possible that this disease is analogous to such disorders as congenital pyloric stenosis and congenital bladder-neck obstruction.

The essential clinical picture is of attacks of an obstructive type of jaundice occurring first in infancy. The course of the disease is chronic and intermittent. Between attacks the patient's colour is normal and the general health is good. The jaundice is accompanied, in most cases, by aching upper abdominal pain, and fever due to infection in the biliary tract. In 90 per cent of cases a cystic tumour, often very large, becomes palpable in the upper abdomen.

Untreated, the condition is fatal due to ascending cholangitis, hepatic cirrhosis or general peritonitis following on rupture of the cyst.

Anastomosis of the cyst to the duodenum, preferably in one stage, cures the condition and has been performed by Gross in a number of cases with a mortality of only 9 per cent. Other methods of treatment have been tried, for example external drainage of the cyst, the gall-bladder or the hepatic duct, and excision of the cyst with anastomosis of the hepatic duct to the duodenum or jejunum. These measures have been uniformly unsuccessful with a mortality-rate of nearly 100 per cent.

The patient whose case is reported below was admitted to hospital at the age of 15 years with biliary peritonitis due to perforation of a congenital choledochous cyst. This is a very rare complication of the disease, and it led, ultimately, to the patient's death.

Another unusual feature of the case was the dilatation of the pancreatic ducts. Calculi were present in these ducts and had, presumably, formed as a result of stasis in the widened channel.

CASE REPORT

A girl aged 15 was admitted to Addenbrooke's Hospital (N.17281) as an emergency with a complaint of abdominal pain which had been present for four days. Her relevant past history went back to the age of eight months when she was ill for a week with jaundice, diarrhœa, and pale stools. At the age of 14 months there was a similar attack, and, when 1½ years old, she was admitted to hospital as she was jaundiced once more. This attack lasted six weeks; again the stools were pale while the urine was noted to be dark. She was found to be a normally nourished child. The liver was palpable but the spleen was not. Occult blood was detected in the stools and the presence of bile in the urine was confirmed. The jaundice faded steadily and she was discharged without a definite diagnosis having been made.

Following this illness she remained well until, at the age of fifteen years, she was admitted to hospital as an emergency. Six days before admission she complained of sore throat and headache. She was recovering from this when, two days later, she complained of bilateral epigastric pain and vomited. The pain and vomiting continued and, eighteen hours before she was seen, became suddenly very much more severe. The pain continued to be very bad and some blood was noticed in the vomitus.

ON EXAMINATION.—She was found to be a thin, very ill child, pale, and sweating. She complained of pain in the abdomen and left shoulder. Her temperature was 98·4° F. (oral), her pulse 140/minute and her blood-pressure 70/?. She was not obviously jaundiced.

The Abdomen.—Slight distension. Generalized rigidity and tenderness. Signs rather less marked in the left lower quadrant than elsewhere. The flanks were dull to percussion. No peristaltic sounds were heard on auscultation.

The Urine.—Contained a trace of bile.

PROGRESS.—A blood transfusion was given and, the patient's condition having improved slightly, laparotomy was performed. The pre-operative diagnosis was general peritonitis of unknown cause.

OPERATIVE FINDINGS.—The peritoneal cavity contained a large quantity of deeply bile-stained fluid in which there

FIG. 14.—Sinugram. The dilated common bile-duct is seen filled with opaque medium, none of which flows into the duodenum. The blurring of the outline of the upper and lateral borders of the shadow is due to opaque medium lying outside the common bile-duct in the hepatorenal pouch. The right border and transverse process of the second lumbar vertebra are obscured by the shadows of calculi which lie in the head of the pancreas.

FIG. 15.—Sinugram. The common bile-duct is less well filled than in *Fig.* 14 but the opaque medium has outlined the undilated common hepatic and right and left hepatic ducts.

were pus and fibrin clots. The gall-bladder was normal and not distended. The lesser omentum and the tissues around the second part of the duodenum were œdematous and markedly bile stained. The second part of the duodenum was mobilized by dividing the peritoneum on its lateral side. No perforation was found. The front of the common bile-duct was seen. No perforation found. A drain was put down to the region of the foramen of Winslow and led out through a flank incision. The abdomen was closed.

POST-OPERATIVE PROGRESS.—*First to sixth days*: There was gradual improvement. Bile drained freely from the flank drainage incision and some fat necrosis of the subcutaneous tissue at this site occurred. This and the fact that some diastatic activity was found in the fluid made it clear that the discharge consisted of a mixture of bile and pancreatic juice. *Sixth to eighth days*: Sinugrams made by injecting Viskiosol 6 into the drainage wound through a catheter (*Figs.* 14, 15, and 16). The opaque medium ran first into a cavity which was situated posteriorly, just in front of and to the right of the first lumbar vertebra. From there it entered a large sac which was thought to be the gall-bladder but which is now known to have been the common bile-duct. Some of the medium refluxed into the hepatic ducts which were not distended. Some calculi were seen and these were thought to be in the pancreas. *Ninth day*: Thirty-three ounces of bile collected from flank drain. She was having her bowels open and the stools had been of normal colour but this day they were noted to be paler than before. *Fifteenth day*: No bile in stools. Slightly jaundiced. Less well. Bilious drainage 11 oz. *Nineteenth day*: A sudden deterioration in her condition occurred and she vomited two or three times in the afternoon. No complaint of pain.

FIG. 16.—Combined sinugram and barium meal. A lateral view showing the flask-shaped choledochous cyst lying between the stomach shadow anteriorly and the opaque medium in the hepatorenal pouch posteriorly. Directly above the cyst, opposite the twelfth thoracic vertebra, is seen the junction of the right and left hepatic ducts.

ON EXAMINATION.—Pulse 160. T. 99·2° F. B.P. 60/? Slightly jaundiced.

Abdomen.—Slight fullness in right hypochondrium. No rigidity. Dull to percussion all over. Rebound tenderness present. A few bowel sounds heard.

3 *hours later*: Pulse 160. B.P. 55/?

Abdomen.—Increased distension in epigastrium and right hypochondrium. Blood draining from flank fistula. A blood transfusion was started and, two hours later, the abdomen was reopened.

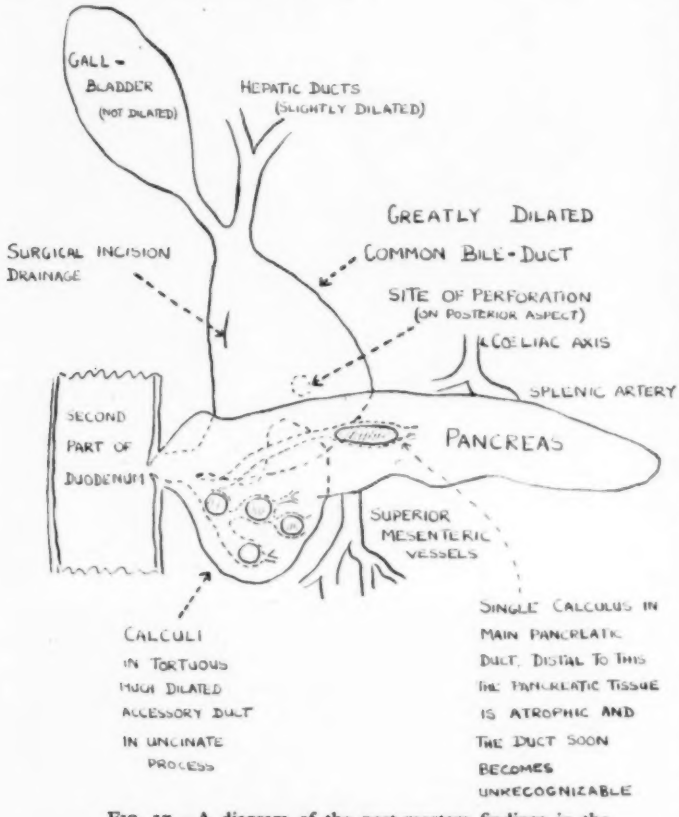

FIG. 17.—A diagram of the post-mortem findings in the biliary tract and the pancreas. The uncinate process of the pancreas extended up behind the choledochous cyst which lay concealed behind the lesser omentum.

OPERATIVE FINDINGS.—No free fluid. Morison's pouch contained old blood-clot mixed with bile. A finger passed into the foramen of Winslow released a gush of infected blood-clot and this was followed by furious bleeding from the region of the foramen of Winslow. The exact source of the bleeding could not be found. It was controlled by packing the foramen of Winslow tightly with gauze.

The gall-bladder was not distended.

The common bile-duct was opened. It was not noted to be distended. A probe was passed down it and entered the duodenum with ease.

The common bile-duct was closed round a T tube, the gauze pack left in the foramen of Winslow and the abdomen closed.

POST-OPERATIVE PROGRESS.—Satisfactory until nine hours after the operation, when the patient collapsed and died suddenly.

AUTOPSY REPORT (Dr. A. M. Barrett).—

Macroscopic.—

The main findings were :—

1. Biliary peritonitis due to a rupture of a fusiform dilatation of the common bile-duct.
2. Secondary hæmorrhage from the portal vein.
3. Calculi in dilated pancreatic ducts.

Relevant extracts from the detailed post-mortem report are as follows :—

The body was that of a well-developed girl with considerable jaundice of skin and conjunctivæ.

Alimentary System.—Great fusiform dilatation of common bile-duct (7·5 cm. circumference at its widest point (*Fig.* 17)). The right border of the common bile-duct is approximately in its normal position, but the left border is much nearer the midline than usual, so that the dilated bile-duct lies behind the head and tip of the uncinate process of the pancreas. The orifice of the papilla of Vater in the duodenum is not obviously enlarged, and a distinct raised ridge on the inner surface of the bile-duct about 1·5 cm. from the orifice apparently represents the limit of the ampulla of Vater. A recent surgical incision containing a few sutures is situated on the anterolateral aspect of the common bile-duct about 3 cm. below the junction of the cystic duct and common hepatic duct, and there is a ragged perforation (0·4 cm. diameter) on the posterior aspect of the duct about 3·5 cm. below the junction of cystic and hepatic ducts. The tissues around this perforation are bile-stained and show evidence of fibrinopurulent inflammation. No calculi found anywhere in biliary tract. Absence of spiral valve in normal sized cystic duct (1·0 cm. circumference). Velvety purple brown mucosa in gall-bladder (7·5 cm. long, 3·8 cm. circumference at widest), which is not dilated and has a wall which is within the normal range of thickness, though apparently thicker than the average. Slight dilatation of lower end of common hepatic duct (1·7 cm. circumference); no dilatation of intrahepatic bile-ducts. Greenish purple cut surface, with indistinct lobular pattern, in large liver.

The accessory and main pancreatic ducts have a common opening into the ampulla of Vater at a point 1·2 cm. from the orifice into the duodenum. The accessory duct is tortuous and much dilated, and at least half a dozen rough-surfaced white calculi (largest about 0·7 cm. diameter) are present in it and its branches in the uncinate process. The main pancreatic duct contains a single fusiform calculus situated 5·5 cm. from the papilla of Vater; proximal to this the duct is slightly dilated and the pancreatic tissue well developed and firm, with conspicuous lobulation; distal to it the duct soon becomes unrecognizable and the pancreatic tissue is flabby, atrophic, and partly replaced by fat.

A ragged perforation is present in the wall of the portal vein (1·5 cm. from the junction of splenic and superior mesenteric veins), on its posterior aspect and near to the perforation in the common bile-duct. Ante-mortem thrombus in the portal vein near the perforation has not extended either into the hilum of the liver or back into the splenic or superior mesenteric veins. Surgical gauze is packed into the foramen of Winslow at the site of the ruptured portal vein; only small amounts of blood and clot are present (about 40 ml. in peritoneal cavity). Obliteration of greater part of lesser sac by fibrous adhesions. Few adhesions between terminal ileum, appendix, and cæcum. Many fibrinous adhesions and strands of fibrin on under-surface of liver. No fat necrosis seen. Mouth, tongue, œsophagus, and stomach normal. Several ill-defined purple red areas (3 cm. diameter approx.) in wall of terminal ileum and cæcum.

Spleen.—Splenic and mesenteric veins patent on dissection. The spleen is slightly enlarged (215 g.) and firmer than normal. The cut surface is purple brown without clear pattern.

Microscopic.—

Common Bile-duct.—Well-developed muscle bundles, both circular and longitudinal, are present in the wall of

the lowest 1 cm. or so of the common bile-duct, and an isolated group of similar bundles about 1 cm. further up. There is little doubt that the amount of muscle is considerably more than in the average normal bile-duct, but one cannot be certain that it is outside the range of normal variation (*Fig.* 18).

Pancreas (*head*).—No significant abnormality; possibly a slight increase in interstitial tissue.

Pancreas (*tail*).—Well-preserved islets of Langerhans embedded in fibro-fatty connective tissue; absence of exocrine secretory tissue.

COMMENT

Perforation of a congenital choledochous cyst has been reported five times before (Blocker, Williams, and Williams, 1937; Kong, 1951; Parkes Weber, 1934; Walton, 1939, Wright, 1935). In Walton's, Parkes Weber's, Kong's, and in the present case the rupture appears to have occurred spontaneously. In the cases of Wright and Blocker and others the rupture was caused by trauma, namely a fall off a bicycle and a fall from a swing. Walton's and Parkes Weber's cases were not operated on, the diagnosis only being made at autopsy. The case of Blocker, Williams, and Williams was operated on and biliary peritonitis was found. As in the present case, the cyst was not a very large one and the cause of the biliary peritonitis was not established. The abdomen was drained but the patient did not recover. The fact that relatively small cysts can rupture is important and makes diagnosis of the condition at operation difficult. Even at the second operation, in the present case, although the common bile-duct was opened, probed, and drained the true nature of the lesion was not appreciated. An added obscuring factor was that the common bile-duct was enlarged in a medial direction only so that the 'cyst' was concealed behind the lesser omentum.

To Professor Kong of the Sun-Yat-Sen University, Canton, goes much credit for having correctly diagnosed a ruptured choledochous cyst at operation and for carrying the case through to a successful conclusion. His treatment was simple drainage of the cyst. The resulting biliary-cutaneous fistula closed spontaneously. The cyst in this case was a large one ('kindskopfgrosse') so that the diagnosis was simplified, but the situation was complicated by the fact that twenty specimens of *Clonorchis sinensis* were found swimming in the contained fluid. The reported follow-up of this case was only for a few months and the ultimate fate of the patient is not known.

Biliary peritonitis is a rare condition. Perforation of a congenital choledochous cyst is a possible cause, especially in a child. In such a case there is likely to be a history of recurring attacks of obstructive jaundice dating back to infancy. Undoubtedly, the correct treatment is external drainage of the cyst, the presence of which may not, at first sight, be obvious. As soon as the patient is sufficiently recovered, the diagnosis of the condition can be established for certain by radiographical studies, after which the biliary-cutaneous fistula should be closed and a permanent choledochoduodenostomy established.

SUMMARY

A short account of the main features of congenital choledochous cyst is given.

A case of biliary peritonitis due to perforation of such a cyst is described. Although the patient recovered from this incident, secondary hæmorrhage from the portal vein led to her death.

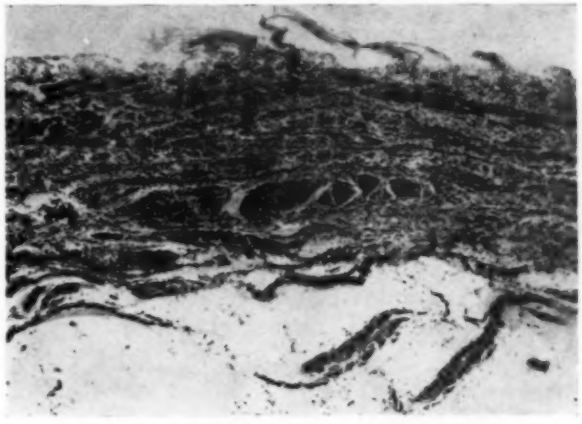

FIG. 18.—A section through the wall of the undilated part of the common bile-duct below the cyst. Well developed muscle bundles, both circular and longitudinal, can be seen. (× 24.)

The true nature of the condition was not appreciated until a post-mortem examination had been made, due to the fact that the cyst was a relatively small one and was concealed behind the lesser omentum.

Drainage of the common bile-duct at the first operation with subsequent choledochoduodenostomy would appear to be the most effective procedure in such cases.

I wish to thank Mr. V. C. Pennell, under whose care the patient was admitted, for permission to treat and to report this case; also Dr. A. M. Barrett of the John Bonnett Clinical Laboratories for allowing me to incorporate extracts from his post-mortem report in this paper. I am indebted to Mr. H. R. Bussey of the research department at St. Mark's Hospital for the photomicrograph of the common bile-duct.

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BILATERAL LEIOMYOMAS OF THE EPIDIDYMIS

By I. D. HENDERSON

FROM THE DEPARTMENT OF SURGERY, POSTGRADUATE MEDICAL SCHOOL, LONDON

In a review of the world literature, there are only three recorded cases of bilateral leiomyomas of the epididymis, by Milner and Gilbert (1939), by Foged (1940), and by Gallizia and Marazzini (1949).

These, together with the present case, comprise approximately one-quarter of the total number of leiomyomas of the epididymis reported.

CASE REPORT

The patient aged 47 years, married but childless, had accidentally noticed a tumour at the lower pole of his right epididymis six months prior to attending hospital. Of nervous disposition, he was anxious that this should be removed. The tumour was small, painless, and smooth. In the tail of the left epididymis a minute swelling similar to the right side was noted. Examination did not reveal any other abnormality.

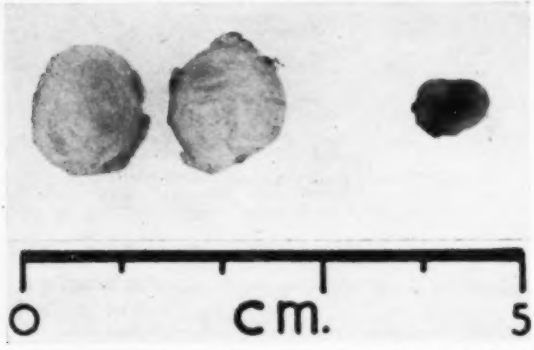

FIG. 19.—The larger leiomyoma from the right epididymis has been completely bisected; the one from the left epididymis has been partially bisected.

On Aug. 10, 1954, through a scrotal incision, a solid tumour 1·5 cm. in diameter was removed from the right globus minor. Recovery was uneventful.

The tumour was spherical and the cut surface appeared white and whorled. Histologically, the diagnosis was simple leiomyoma.

An identical operation was performed on the left side. The second tumour 6 mm. in diameter, was otherwise comparable in all respects with the first. (*Figs.* 19, 20.) When last seen eight months after operation, the patient was well and lacked any signs of recurrence.

DISCUSSION

The benign tumours of the epididymis are rare and by nature of the terminology, used in more than seventy papers describing them, exceedingly confusing. The commonest benign tumour has been named variously adenomatoid tumour, mesothelioma, lymphangioma, mixed leiomyoma and lymphangioma, adenomyofibroma, fibromyoma, adenocarcinoma, hamartoma of mesonephric origin, and various others.

Sundarasivarao (1953) has produced strong evidence that this tumour is epithelial and derives its origin from Müllerian duct remnants. From its histology a myoadenoma of the paramesonephros would seem to be the most suitable name. Of this tumour, there are more than 90 cases reported as arising in the epididymis.

The next most common benign tumour is the leiomyoma, of which 17 cases have been reported to the end of 1954. A number of the authors have considered this to be merely a variant of the myoadenoma. This is incorrect on histological examination and probably on natural history. Study of multiple sections of the present case and of the photomicrographs, or reports of the previous cases, has failed to reveal any evidence of the presence of adenomatous structures. With the inclusion of the present case, 4 of 18 cases have been bilateral, whereas all the myoadenomas have been solitary. In the female, according to Lee, Dockerty, Thompson, and Waugh (1950) only 12 cases of genital myoadenoma were found in more than 8300 hysterectomies and myomectomies, and in each case as a solitary finding, though there were associated leiomyomas in 9 of the cases.

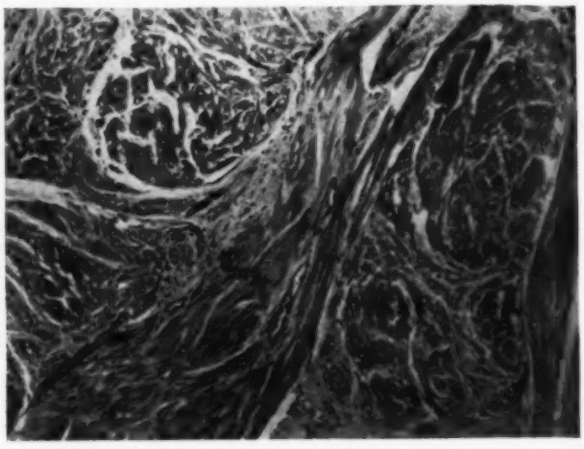

FIG. 20.—Photomicrograph left of the epididymal leiomyoma. No adenomatous structures were seen on multiple section. (× 85.)

Other benign tumours occurring in the epididymis are excessively rare and include lipoma, cholesteatoma, and adrenal cortical adenoma.

Lazarus and Friedman (1954) were able to note 52 cases of malignant tumours of the epididymis up to 1952. It follows that benign tumours of this organ are twice as common as malignant ones.

In the British literature, the statement has frequently been made that the leiomyoma is the commonest tumour of the epididymis. From the aforementioned figures this statement is wrong, and the tumour arising from Müllerian duct remnants is more than five times as common.

SUMMARY

A case of bilateral leiomyoma of the epididymis is reported. It is suggested that the commonest benign tumour of the epididymis should be called a myoadenoma.

Evidence is produced that this is not a variant of the leiomyoma.

Figures show that benign tumours are twice as common as malignant tumours of the epididymis and that malignant tumours are three times as common as leiomyomas of the epididymis.

I would like to thank Mr. R. Shackman for permission to treat and report this case, and the Departments of Pathology and Photography for the reports of the microscopy and the photographs.

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LARGE SOLITARY CYSTS OF THE PARATHYROID GLAND

BY W. MILO KEYNES AND BRIAN MCN. TRUSCOTT, CAMBRIDGE

LARGE, solitary, unilocular cysts of the parathyroid are rare, although cystic areas in parathyroid adenomata and microscopic cystic areas in apparently normal parathyroid glands are not uncommon. These large cysts are distinguished from other cysts in the neck by the presence of typical parathyroid cells in the cyst wall, in most examples a cyst lining of cuboidal or columnar epithelium, and by the fact that they lie in the position normally occupied by a parathyroid gland (McGoon and Cooley, 1951). For these reasons they seem to be a separate entity from other cysts of branchial origin.

FIG. 21.—Photomicrograph of part of the infolded wall of a large parathyroid cyst. The flattened epithelium lining the cyst is shown with a mass of parathyroid tissue in the wall. Hæmatoxylin and eosin. (× 52·5.)

The case reported below would appear to be the fourteenth recorded and the first in British literature. Cope (1955) in a personal communication informs us of one more.

CASE REPORT

In May, 1955, a spinster, aged 40, was seen by Dr. L. C. Martin with a lump in the left side of the neck which she had accidentally noticed five weeks before and which she thought varied in size but was slightly enlarging. The lump was painless and caused no symptoms.

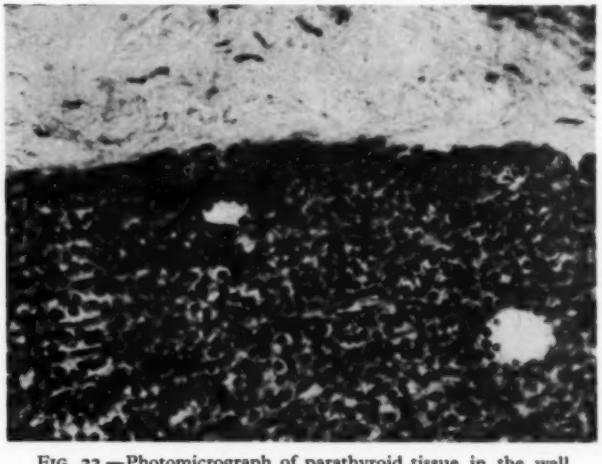

FIG. 22.—Photomicrograph of parathyroid tissue in the wall of a large parathyroid cyst. Hæmatoxylin and eosin. (× 255.)

ON EXAMINATION.—Apart from a mild hypertension and low cerebration, there were no abnormalities except

for a lump in the region of the left lobe of the thyroid gland which was causing a slight deviation of the trachea to the right. The lump was firm, about the size of a hen's egg, and moved on swallowing. It did not extend behind the sternum. The right lobe of the thyroid could just be felt. A pre-operative diagnosis of a nodular goitre involving the left lobe of the thyroid was made. The patient was anxious to have the lump removed.

At Operation (B.M.T.).—On May 31 the usual incision for exposing the thyroid gland prior to a partial thyroidectomy was made. On dividing the strap muscles on the left side it quickly became apparent that the lump, which had been regarded as a thyroid tumour, was in fact distinct from the thyroid and consisted of a large, thin-walled cyst which was pushing a normal left lobe of the thyroid upwards from its usual site. There were no macroscopical pathological changes apparent in the thyroid gland as a whole. Removal of the cyst was easily achieved by blunt dissection and it was found to measure 5 cm. by 4 cm. On opening the cyst the fluid was of a thin, slightly milky consistency. On section the cyst was lined by a flattened epithelium and with islands of cells resembling parathyroid tissue in its wall. (*Figs.* 21, 22.)

DISCUSSION

With the present report there are 13 similar examples in the literature (Goris, 1906; Anzilotti, 1909; de Quervain, 1925; Nylander, 1929; Welti, 1946; McNight, 1946; Black and Watts, 1949; McGoon and Cooley, 1951; and Maxwell, Horn, and Rhoads, 1952). Probably other examples have not been recorded since the last three of these nine papers each record more than one case.

Position.—Eleven of the 14 cysts have been found in the region of the inferior parathyroid gland; 1 was in the position of the right superior parathyroid gland, 1 in the superior mediastinum, and 1 in the upper part of the neck between the sternomastoid and angle of the jaw. Five of the cysts have extended inferiorly into the mediastinum.

Size.—The reported size has varied from 1 cm. in diameter to 7 cm. by 3 cm.

Symptomatology.—The presenting symptom in all cases has been a lump in the neck which has been diagnosed almost invariably as a nodular goitre. In 1 case the cyst was found as an incidental finding during a thyroidectomy for secondary thyrotoxicosis (McGoon and Cooley, 1951), and 1 was discovered during removal of a typical parathyroid adenoma causing hyperparathyroidism from the opposite side (Black and Watts, 1949). Welti (1946) noted the possibility of a recurrent laryngeal nerve palsy on the side of a cyst. In no instance has tetany followed the removal of a cyst.

Aetiology.—The origin of these large parathyroid cysts is not clear. They may be formed by retention of secretions in the colloid vesicles so frequently found in normal glands (Gilmour, 1939; McGoon and Cooley, 1951), or they may be derived from a congenital cyst originating from the third or fourth pharyngeal pouch and arising in or around a parathyroid gland, that is as a pharyngeal pouch remnant located near a parathyroid gland which secondarily incorporates the parathyroid in its wall. Against this latter theory, however, there have been reports of the surgical removal of cysts in the region of the parathyroid glands which had no demonstrable parathyroid tissue in their walls (Welti, 1946; Black and Watts, 1949; Maxwell and others, 1952). Also in favour of the first theory is the finding of Gilmour (1939), who, in 428 autopsies, found small cysts visible to the naked eye in 11 parathyroid glands, all of which were inferior glands. As already mentioned, the majority of the large parathyroid cysts removed have been located in the region of the inferior glands.

SUMMARY

Microscopic cysts commonly occur in parathyroid glands and larger parathyroid adenomata may be partially cystic. In this paper a large parathyroid cyst is reported, with a short review of 13 similar examples. Such cysts are distinguished by typical parathyroid cells in the cyst wall, a cyst lining of cuboidal or columnar epithelium in most examples, and a position in the neck corresponding to that of a parathyroid gland and independent of the thyroid gland. It is for these reasons that they are separated from other cysts of branchial origin. Their origin is not clear; functionally they are of no significance and only give symptoms as space-occupying lesions. The usual pre-operative diagnosis is a nodular goitre and removal has been easy.

We are indebted to the staff of the Department of Pathology, University of Cambridge, for the histological report and photographs.

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THE MANAGEMENT OF THYROTOXICOSIS

By VICTOR RIDDELL
ST. GEORGE'S HOSPITAL, LONDON

It is now twenty-six years since the subject of toxic goitre was reviewed in a memorable contribution to this JOURNAL by Sir Thomas Dunhill (1930). In the intervening years the whole outlook for the patient with thyrotoxicosis has been transformed by the discovery and introduction of two new therapeutic weapons, the antithyroid substances and the radioactive isotope of iodine (I^{131}).

There are therefore now available three methods of treatment for thyrotoxicosis which may be called the surgical (short-term), the pharmacological (long-term), and the radiotherapeutic.

The decision as to which of the three methods is best suited to his patient can be a perplexing problem for the clinician responsible for the management of a case of thyrotoxicosis. It is the object of this paper to suggest how the selection process may be applied in practice. The definitive treatment, whether by medicine or surgery, is a relatively simple matter to implement and supervise, but if the initial process is at fault a wrong course of treatment may be set in motion or, as can easily happen, a diagnosis of thyrotoxicosis is made where none exists.

I have also tried to place in perspective such expressions of opinion as "Every patient with thyrotoxicosis should be given an antithyroid agent", "Operate on every nodular goitre", "Never (or always) ligate the inferior thyroid arteries", and other generalizations of a similar kind.

Finally, a special point has been made of presenting the *medical* aspects of the management of thyrotoxicosis, including the purely medical as well as the pre-operative use of the antithyroid agents. These drugs, while ultimately easing the achievement of a euthyroid state, can complicate the pre-operative phase and indeed the operation itself. It is incumbent therefore upon the surgeon, both for his own peace of mind and the good of his patient, that he should be entirely familiar with the potentialities and eccentricities of these powerful agents.

Continuity of Supervision.—The barrier which has grown up between medical and surgical methods is highly artificial. It is essentially due to a lack of familiarity with what, in practice, are often alternative methods of management. The treatment of the toxic thyroid gland can only be applied to the best advantage of the patient if surgeon and physician are absolutely familiar with all the details and vagaries of both methods of treatment. Such a true understanding of the disease by surgeons can only come about if they are prepared to make a special study of the medical methods of management and of the results so obtained. It is only with this experience to draw upon that the relative merits of the two forms of treatment can be properly assessed in a particular case and the patients most suitable for surgery and the optimum moment for surgery be chosen with reasonable accuracy. The divided responsibility—for success of failure—which comes from an initial medical control and subsequent surgical intervention by another individual who is a stranger to the patient is a serious weakness in the management of these patients.

From this it follows that it is essential for the surgeon to see the patient in her *original thyrotoxic state*, that is, at her worst, and before therapy is initiated. If seen for the first time when an antithyroid effect has been obtained, an entirely false assessment of the severity of the disease may be made and a wrong decision come to as to the need or time for operative treatment.

FIG. 23.—Robert James Graves, 1796–1853.
(*From a statue in the Royal College of Physicians of Ireland.*)

The subject is discussed under the following main headings :—

Nomenclature of Toxic Goitre.
Aetiology of Toxic Goitre.
The Antithyroid Agents.
Complications of Antithyroid Therapy.
THE MANAGEMENT OF THYROTOXICOSIS
Part I. The Form of Treatment
Medical Group
Surgical Group
Indeterminate Group

Part II. Definitive Treatment
General Management
Short-term Therapy—Surgical Treatment
Long-term Therapy—Medical Treatment
Radio-active Iodine
The Operation
Post-operative Complications
SUMMARY

NOMENCLATURE OF TOXIC GOITRE

Before proceeding further it is necessary to agree upon a nomenclature for toxic goitre. It is convenient to retain the terms ' primary thyrotoxicosis ' (toxic diffuse goitre) and ' secondary thyrotoxicosis ' (toxic nodular goitre), although the one merges imperceptibly into the other, if for no other reason than that the extreme examples of these two varieties usually require different management. Secondary thyrotoxicosis is better called ' toxic nodular goitre ' because it is the nodular element which differentiates this group from the primary toxic goitres and is responsible for the special treatment (usually surgical) which these patients may require. The solitary toxic nodule or hot nodule of some authors will continue to be called ' toxic adenoma '.

The familiar titles ' Graves' disease ' (Parry's disease, Basedow's disease) and ' exophthalmic goitre ' will not be used in this article. Reluctant though one is to discard the traditional and historical, the fact is that many patients do not show exophthalmos or even a goitre; and the different interpretations of what Graves meant (1835) (*Fig.* 23), and of what we mean to-day by Graves' disease, only add confusion to this already complex subject. The terms ' toxic diffuse goitre ' and ' toxic nodular goitre ' have the simple clinical advantage of describing what we can see and no more.

Although this distinction between the two varieties of thyroid intoxication is somewhat grudgingly accepted on grounds of clinical convenience, general opinion is still on the side of a common pathological basis for both. The same abnormal stimulus is believed to cause a previously normal thyroid to produce primary thyrotoxicosis and to supervene upon a simple goitre producing toxic nodular goitre (secondary thyrotoxicosis). The clinical similarities are held to support the identity of the thyrotoxic process in both, but the differences are regarded as sufficient to warrant a distinction for the practical purposes of treatment. As Martin and Fisher (1951) say, " this is an illogical state of affairs which arises ultimately from our ignorance of the fundamental mechanisms of thyrotoxicosis, and from misinterpretation of the histological appearances in the thyrotoxic thyroid gland. Because the thyroid epithelium is hyperplastic in both primary and secondary thyrotoxicosis, it has been assumed in the past that the causal thyrotoxic stimulus has been the same in both types. But this assumption may well be incorrect, for the thyroid epithelium may be hyperplastic in a variety of other circumstances, which include simple iodine deficiency, compensatory hyperplasia after partial thyroidectomy, and the administration of thiouracil drugs. It is not justifiable, therefore, to base conclusions as to the cause of epithelial hyperplasia of the thyroid upon histological examination, and we have no concrete evidence for assuming that the hyperplastic epithelium observed in primary and secondary thyrotoxicosis is produced by the same stimulus. The elucidation of the pathogenesis of primary and secondary thyrotoxicosis is more likely to be furthered by closer examination of their differences than by continued emphasis on their similarity." The demonstration of hereditary influence in the development of primary thyrotoxicosis (Martin and Fisher, 1945) and the lack of evidence for it in secondary thyrotoxicosis (Martin and Fisher, 1951) certainly do not favour a common cause of both. The position can be summarized by saying that in the uncertain light of present knowledge we should continue to keep an open mind before accepting as proven the identical nature of the thyrotoxic process in primary and secondary thyrotoxicosis.

AETIOLOGY OF TOXIC GOITRE

The cause of thyrotoxicosis remains unexplained. It would certainly seem that it is related to overproduction of the thyrotropic hormone of the pituitary and that the act of toxicity does not spring primarily from a disorder of function in the thyroid gland itself. The primary seat of the trouble may, however, occasionally be in the thyroid, as in the case of the solitary ' toxic adenoma ', and in such patients a complete cure may be achieved. More often the cause or causes lie outside the thyroid gland, perhaps in the pituitary or other elements of the endocrine system, and these sources and situations are at present less vulnerable to successful attack and rational treatment, for the antithyroid drugs, radioiodine, and operation all act at the level of the thyroid gland itself.

Heredity, sex, stress, diet, and a previously present goitre may each at times play a part. The incidence of toxic goitre is highest in individuals of unstable personality. It is said that no great statesman is known to have suffered from thyrotoxicosis, but it is certainly not uncommon in the highly cultured and artistic. Unstable personalities, if exposed to anxiety, responsibility, or emotional stress, are more likely to break down than others, and one way in which they may do so is by developing thyrotoxicosis. Our aim should be to reinstate the patient into thyroid balance. One cannot expect to alter a naturally excitable or unstable temperament.

Nodular Goitre and Toxic Change.—There is no doubt that a person in whom a goitre is already present is more likely to develop thyrotoxicosis than a person who has no goitre. States with a high incidence of endemic goitre like Tasmania (Stuart, 1955) and New South Wales have a much higher death-rate from thyrotoxicosis than Western Australia where endemic goitre is almost non-existent (Clements, 1954). Some would go so far as to say that sooner or later every nodular goitre develops some toxic features (Linnell, 1945). Support is lent to this view by one's experience that patients with a simple goitre showing no clinical evidence of toxicity frequently develop a transient auricular fibrillation following operation, whereas non-goitrous patients who are operated upon rarely do so. Certainly an apparently non-toxic goitre in a middle-aged or elderly patient should be treated with respect and

the fact remembered that it may have latent toxic potentialities which, although subclinical before operation, may be released post-operatively.

If, however, the threat of toxicity were the only hazard facing the patient with a nodular goitre it would hardly be justifiable to-day to advise a prophylactic thyroidectomy on these grounds alone, for the toxicity if it developed, and it might not, could easily be controlled with one or other of the weapons in the antithyroid armoury. There is, however, another development that cannot be divorced from our deliberations when we are weighing the pros and cons of conservative treatment versus thyroidectomy in patients with nodular goitre—namely, the possibility of malignant change in a simple nodular goitre.

Nodular Goitre and Malignant Change.—The relationship between endemic goitre and cancer of the thyroid is no longer a question of speculation and conjecture. Wegelin (1928) reported that in 13,426 autopsies carried out in Berlin, only 13 (0·09 per cent, or 1 in 1033) malignant thyroid tumours were found, whereas in 15,250 autopsies in Berne, 159 (1·04 per cent, or 1 in 96) thyroid tumours were found. This comparison has the statistical advantage of dealing with large numbers. The striking contrast between the figures for Berne and Berlin can be explained only by the fact that Berne is the centre of a district in which endemic goitre reaches its maximum intensity in Europe, while Berlin is a city almost free from goitre. The remarkable fall in the incidence of thyroid cancer in Switzerland since the compulsory iodization of salt in that country cannot be ignored (Wynder, 1952), nor can the effect of iodine deficiency in the experimental animal be passed over. In the rat iodine deficiency results in an increased production of thyroid stimulating hormone (T.S.H.), which in turn results in thyroid hyperplasia which in a significant number of cases goes on to thyroid carcinoma. (Axelrad and Leblond, 1953; Doniach, 1954.)

In spite of this strong but not absolutely conclusive evidence and the observations of Branson and Houston (1949), I feel that there is still a place for the exercise of judgement and conservatism in the individual case. It is certain that very few nodular goitres become malignant, and of those that do—of the endemic type—the path to malignancy is slow. When it happens, it does not invariably constitute a danger to life. Survival times of ten years and more in untreated cases of papillary carcinoma are not exceptional (Bielschowsky, 1955). Moreover, if cancers of the thyroid often arose in adenomas one would expect to find the highest incidence of cancer in large multinodular goitres: the reverse is true, for cancer occurs most commonly as a solitary tumour of the thyroid, and solitary tumours occur predominantly in patients of the younger age group (Crile, 1954).

Before recommending the indiscriminate application of subtotal thyroidectomy to all non-toxic goitrous patients, one would need to show that the proposed remedy was less lethal than thyroid cancer itself. One should reflect that statistics favouring its widespread adoption are not based on an equally widespread analysis of all patients with nodular goitre, but only on that selective group who seek medical advice. Furthermore, cancer of the thyroid in this country forms less than 1 per cent of all cancers, so that a great many operations would have to be carried out to save one patient from developing cancer of the thyroid and this might be possible only at the cost of an operative mortality which was nonsensical.

To summarize—I think our attitude towards multinodular goitre (non-toxic), in spite of the twin risks of toxic or malignant change, should not be inflexible. While there should be a bias towards surgery, especially in the coarsely nodular variety, numerous cases undoubtedly occur where the nodularity is not marked and where observation only is justifiable—provided operation is undertaken immediately any physical change in the size of the gland is detected. One has only to have seen this change ignored in goitres which have been present for many years to be much influenced by the hopelessness and futility of a position which neglect forces upon both patient and surgeon.

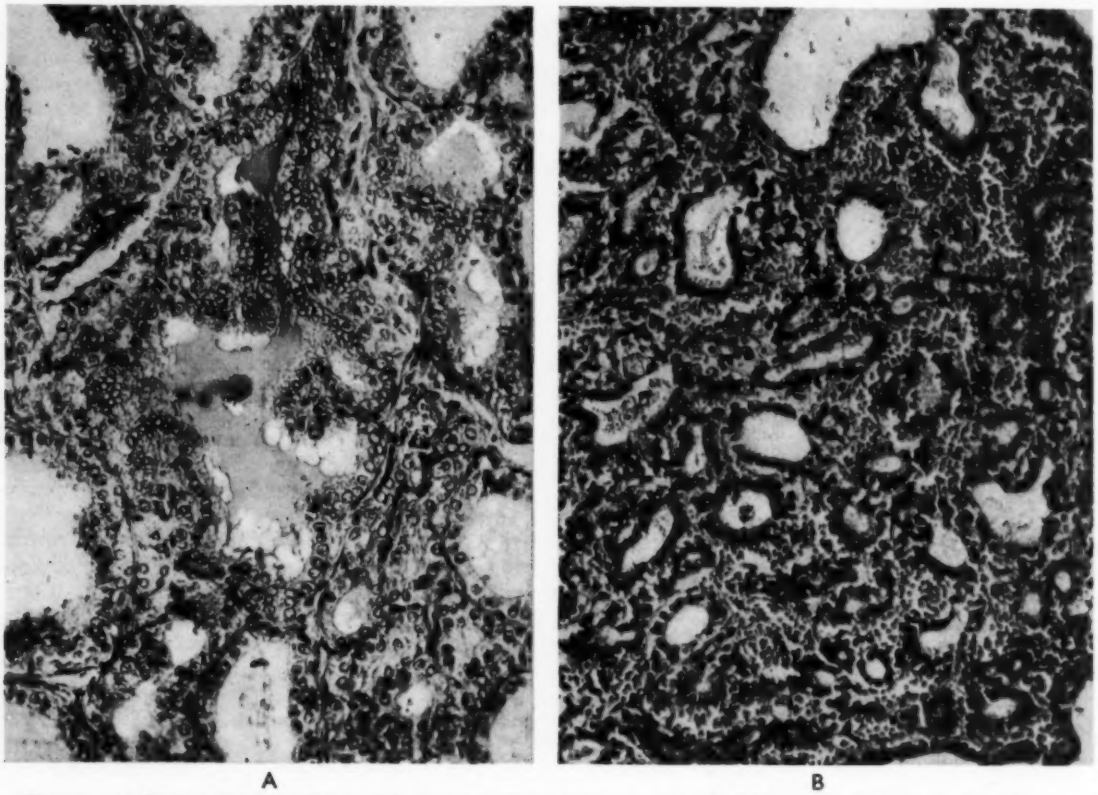
THE ANTITHYROID AGENTS

Errors of Judgement.—We have now had a considerable experience of the antithyroid group of compounds. It is not surprising that during the period of their development mistakes have been made in their application. There have been errors in regard to the patients selected for treatment, and there have been errors of dosage. We know that by no means all patients with thyrotoxicosis benefit from or require the administration of antithyroid substances. We know also that there has been a tendency to give antithyroid agents in dosage that was too high, or for periods that were too short or too long. Too often I know that I have given preoperative antithyroid agent when the patient could have been brought to a perfectly safe operative level with iodine alone (as so many were in the prethiouracil days), and too often in those severe cases requiring pre-operative antithyroid agent one has continued the administration unnecessarily long and thereby increased one's own difficulties at the operation. We are now aware of these errors of judgement and so should be able to avoid repeating them.

Favourable Features.—The antithyroid drugs have ushered in a new era of safety in thyroid surgery: they have abolished the fear of post-operative thyroid crisis except in those few cases which are resistant, and they have rendered obsolete in all but the most exceptional instances the need for individual ligation of arteries and multiple-stage operations. But above all else, by enabling us for the first time to fulfil our main pre-operative objective—the conversion of a toxic into a non-toxic goitre—they have removed much of the hazard and increased the accuracy of the operation.

These altered circumstances of added safety in which thyroid surgery is conducted to-day must be borne in mind when comparing and contrasting the merits of the purely medical and surgical procedures. The adverse conditions which held prior to 1943, when surgery so often had to be carried out under the unfavourable conditions of uncontrolled toxicity, no longer exist, as a direct result of the introduction of the antithyroid substances.

This event has had its effect upon both patient and surgeon. It is now in our power to make the patient safe for surgery to a degree unknown prior to the thiouracil era. It is also in our power to make surgery safer for the patient, since there is no longer the same necessity for speed in operating as there was in the constitutionally ill and toxic subject. One great advantage which an unhurried operation affords is that it allows time for the individual ligation of the superior and inferior thyroid arteries on each side, thus preparing the way as nearly as is possible for operation in a bloodless field. This in its turn renders injury to the parathyroid glands and recurrent laryngeal nerves less likely and their identification possible if this is thought desirable. Equally important, a more accurate assessment of the amount of gland to be resected can be made—a key decision in the operation—for nothing brings thyroidectomy for toxic goitre into such disrepute as inadequate procedures.



A B

FIG. 24.—A, Papillary adenocarcinoma of the thyroid. (H. and E.) (× 90.) B, Primary thyrotoxicosis treated with propyl thiouracil. (H. and E.) (× 90.) The epithelial activity seen in the section of the thiouracil-treated gland (B) illustrates the extreme complexity of the histology and explains how pathological identification may sometimes err on the side of malignancy.

Unfavourable Features.—There is, however, another side to the picture. The influence of the antithyroid agents is not exclusively favourable. In patients treated medically there is a high relapse rate, and such cases, if eventually referred for surgery are technically much more difficult to operate upon. In those who are controlled by the agent used, the permanence of the stabilization is not yet known. It would seem that the effect, when successful, is more often a holding technique comparable with insulin in diabetes, than a curative measure. The hope is that the attack on the thyroid may coincide with or encourage to develop one of those natural remissions which are so typical of thyrotoxicosis and that after treatment the disease may burn itself out.

The drugs also have toxic side-effects which while usually trivial can occasionally be so serious that their administration has constantly to be supervised, sometimes for months, sometimes for years. Indeed, it is over this question of supervision, or rather continuity of supervision, that the medical treatment can so easily break down, for if it is applied by a series of different advisers, and this is almost inevitable if the treatment lasts as long as a year or more, the personal touch and personal knowledge of the patient and her illness must be lacking. This can reflect only adversely upon the patient and the method of treatment employed. Continuity of supervision by one man is essential in these diseases of psyche and soma, and this demands more time and patience than many are prepared or able to give to their patients.

Carcinogenesis.—Finally there is one uncertainty about the antithyroid drugs which should be a warning to us to avoid treating patients for prolonged periods with these substances. I refer to the possible carcinogenic effect (*Fig.* 24). So far no proven case of goitrogenic induced cancer of the thyroid has been reported in man but in rats numerous instances of metastasizing carcinomas of the thyroid have been recorded either following thiourea (Purves

and Griesbach, 1947) or propyl thiouracil (Sellers, Hill, and Lee, 1953). The determining factor in the development of experimentally induced cancer of the thyroid in rats and mice is thyroid hormone deficiency. Whether this deficiency is due to an insufficient iodine content of the diet or to damage or destruction of the gland by radio-active iodine or thyroidectomy, or is induced by goitrogens which interfere with the mechanism whereby the thyroid synthesizes its hormone (TH), the result is always the same. The pituitary reacts to the lowered thyroxine level, with an increase in the output of its thyroid stimulating hormone (TSH), and the thyroid reacts to thyrotropic stimulation with hyperplasia which is at first diffuse, then nodular, and finally neoplastic (Bielschowsky, 1955). This sequence of events takes a long time even in the rat, and therefore would presumably take many years in man—if indeed such a change can come about, but the possibility is there.

It is significant that all the neoplastic lesions in animals can be prevented by supplying them with adequate amounts of thyroid hormone while the goitrogen is being administered. Therefore, although one cannot argue from animal to man, it might be wise to administer thyroid extract synchronously with the antithyroid agent in all cases in which its use is likely to be prolonged—as has been done by Fraser and Wilkinson (1953) in the hope that this combination may exert a balancing effect upon the pituitary.

Action.—The antithyroid agents most commonly employed are methyl and propyl thiouracil and carbimazole (neomercazole). They block the formation of thyroid hormone within the gland. Their mode of action is to interfere with the synthesis of thyroxin by preventing the union of iodine and tyrosine into diiodotyrosine, which is the precursor of thyroxin. The resultant fall in the production of circulating thyroxin stimulates the anterior pituitary to an increased production of thyrotropic hormone, and this in turn is followed by an ineffectual hyperplasia of the thyroid gland, clinically manifested in a proportion of patients by an increase in its size. The thiouracils and carbimazole do not produce an effect upon the thyroxin already stored in the gland or in circulation, which explains the short time lag before clinical improvement is noticed following its administration.

Requirements.—The ideal antithyroid compound should be non-toxic and quick-acting, and should produce its effect without increasing the vascularity of the thyroid and without producing a goitre. 'Neomercazole' is said to fulfil these requirements more nearly than propyl or methyl thiouracil, and is recommended by Lawson and Barry (1951), Poate (1953), Doniach (1953), and Greene and Morgan (1956). I have used it with effect in 32 cases without a granulopenic toxic reaction and with less enlargement of the thyroid itself than with the other agents, but my impression is that the vascularity of the gland is comparable to that produced by the thiouracils. Doniach (1953) treated 120 patients without any toxic reaction; on the other hand one fatal case of marrow aplasia has been reported by Richardson, Sarkany, and Campbell (1954), and Bartels (1954) reports a case of agranulocytosis which recovered.

Dosage.—*Carbimazole* (*neomercazole*) is administered in a total daily dosage of 20–40 mg. depending on the severity of the thyrotoxicosis, and its administration is controlled in the same way as the thiouracils. Its superiority over these drugs remains to be established by more extended trial, but collective experience suggests that neomercazole may ultimately prove as effective as the thiouracils and less toxic and less goitrogenic. Despite these qualities the fact that agranulocytosis may still follow its administration, however rarely, indicates that the ideal antithyroid drug has not yet been discovered.

Growing experience shows that there is little to choose between methyl and propyl thiouracil. They both produce the same effect in the same time and with much the same reaction rate. It seems probable that the earlier doses used were much too high—the maximum initial dosage should not exceed propyl thiouracil 200 mg. twice a day, and in most cases in my experience an excellent response will be obtained from half this dose (100 mg. b.d.). (The equivalent dose of methyl thiouracil is double the dose of propyl thiouracil.) Because of its availability methyl thiouracil has been used in this country more than the propyl compound, and perhaps for this reason has acquired a reputation for having a higher toxic reaction rate; in practice there is little difference in the respective reaction rates, approximately one in ten patients showing some toxic manifestation. It is, however, worth bearing in mind that a patient who is intolerant to one form of antithyroid agent may respond normally to another, so that after a brief interruption treatment may be resumed with safety in those patients who have not shown a granulopenic reaction.

Potassium Perchlorate.—The treatment of thyrotoxicosis with potassium perchlorate has been investigated by Morgans and Trotter (1954). They found it to be a safe and cheap drug without toxic effects in 108 cases treated. The rate of response was slower than with methyl thiouracil, so that it is unsuitable where rapid action is required and some cases were not controlled by perchlorate, the dose of which is approximately double that of methyl thiouracil. It acts by preventing the thyroid from concentrating iodine, unlike the thiouracils which prevent the synthesis of thyroglobulin. It is unsuitable for use with iodine pre-operatively and is a gastric irritant to some people.

COMPLICATIONS OF ANTITHYROID THERAPY

Toxic Reactions, including Granulopenia and Agranulocytosis.—Toxic reactions following methyl and propyl thiouracil still occur in approximately 10 per cent of patients (in 9 per cent of 358 patients treated with methyl thiouracil by Morgans and Trotter, 1954). A toxic reaction usually occurs within the first eight weeks of treatment, but may arise much later. I have had experience of one as early as the second day and one after two and a half years, so that vigilance can never be relaxed. The common toxic side-effects are drug fever, malaise, nausea, headache, sore throat, loss of taste, enlarged lymph-nodes, swollen joints, and a rash. (A rash may be due to phenobarbitone if this is being taken at the same time, *Fig.* 25.) All forms of toxic reaction are important as *warning* symptoms, but all

do not carry the same potential for danger. The following facts are emerging :—

1. *Toxic Reactions—Two Groups.*—Toxic reactions should be divided—from the point of view of danger and management *and* recording—into those that are accompanied by granulopenia and those that are not. If there is no granulopenia treatment can usually be resumed after the reaction has subsided but if a granulopenia is present, treatment with antithyroid agents may have to be abandoned. In my series 165 patients were treated with antithyroid agents (methyl and propyl thiouracil and neomercazole) : 13 patients developed granulopenia (8 per cent), and in 7 of these medical treatment had to be abandoned altogether ; in the remaining 6, after a suitable interval and changing the antithyroid agent, treatment was continued uneventfully.

FIG. 25.—*Drug rash.* A toxic drug rash developing during the administration of an antithyroid agent.

Van Winkle, Hardy, Hazel, Hines, Newcome, Sharp, and Sisk (1946) reported the side-effects of thiouracil treatment in 5715 patients. The overall toxic reaction rate was 13·1 per cent. Granulopenic reactions occurred in 142 patients (2·5 per cent). Fatal agranulocytosis occurred in 21 patients, establishing a mortality-rate of 0·4 per cent for the entire series and a case fatality-rate for *agranulocytosis* of 14 per cent.

Moore (1946) reported the side-effects in 1091 patients receiving thiouracil. Agranulocytosis developed in 19 patients (1·74 per cent) in the series, and 5 of these patients died as a direct result of the thiouracil treatment, establishing a mortality-rate of 0·4 per cent for the entire series and a case fatality-rate for *agranulocytosis* of 26 per cent.

These figures include the early cases before agranulocytosis was anticipated and before penicillin was used routinely. The present-day mortality is certainly less.

2. *Marrow Depression—Time Interval.*—The most dangerous period from the point of view of granulocyte depression is from 4 to 8 weeks after the initiation of treatment. Approximately 75 per cent occur at this early stage. A delayed granulopenic reaction can also occur some days after stopping treatment, so it is wise when using an antithyroid drug preoperatively to discontinue its use a week before operating and for safety to carry out a blood-count on the day before thyroidectomy.

Clinical Control of Antithyroid Therapy.—Propyl (and methyl) thiouracil are poison to some individuals. This is due to the high concentration which they may reach in the bone-marrow. Although the mortality from agranulocytosis is extraordinarily low considering the widespread use of these goitrogenic agents, the fact remains that any therapeutic measure which carries with it the risk of death, however remote, requires that special precautions be taken in its application. It is curious that the incidence of agranulocytosis is not directly related to the total amount of the drug taken, and in some instances it may be more of an idiosyncrasy than a straight intoxication.

It cannot be too strongly urged that routine blood-counts as a safety method of control are not only useless but *dangerous*, as the drug may strike with dramatic suddenness. Blood-counts which may be normal one day may be seriously leucopenic the next. Fortunately this sudden and dramatic fall rarely, if ever, occurs without warning symptoms. It is for this reason that the *clinical* method of control is recommended. For the clinical method of control to be safe, everyone coming in contact with the drug—patient, nurse and doctor—must be absolutely familiar with its side-effects. If the patient is being treated at home or as an out-patient she should be given a *written* list of the commoner toxic symptoms and instructions to report at once if any of these develop.

In the case of *agranulocytosis* the chain of events may be divided into three periods : In the first there is malaise, fever, and perhaps chill—prodromal symptoms which are often overlooked. In the second there is a period of freedom from symptoms except for fatigue and prostration during which the leucocyte count falls and granulocytes disappear. This is followed by the final stage when, resistance being lowered by the absence of granulocytes, infection occurs in those regions normally harbouring bacteria such as the gums, tonsils, soft palate, and pharynx, and progresses with extreme rapidity in the defenceless tissues. (Wintrobe, 1946.)

Management of Toxic Reactions.—It is imperative that immediate action should be taken upon any of the well-known toxic complications of the antithyroid drugs presenting.

Action will take the form of instantly stopping the administration of the drug, of giving a prophylactic injection of penicillin, and making an immediate examination of a blood-smear. In the latter a formal differential count at this stage—unless the polymorphs are alarmingly scanty—is unnecessary and time-consuming. It is a simple matter for an experienced pathologist to tell from a smear, almost at a glance, whether or not the granulocytes are plentiful. (1) If the granulocytes are *scanty* or there is any anxiety about their numbers, the patient should be admitted to hospital immediately as an emergency.

The subsequent treatment will be dictated by the patient's progress or deterioration; in the latter event every resource will have to be mobilized, including blood transfusion. After the blood-count returns to normal the patient should be put on to iodine and followed up with a subtotal thyroidectomy. (2) If the granulocytes are *plentiful* after a toxic reaction it is sufficient to wait until this has subsided, usually about ten days, and then to switch to another antithyroid agent—for example, from propyl thiouracil to neomercazole. Toxic effects, on a *solitary* occasion, with the exception of granulopenia (and agranulocytosis), do not contra-indicate the continuation of treatment. But if on resuming treatment there is a second toxic reaction, even though not accompanied by granulopenia, serious consideration should be given to abandoning the antithyroid drugs.

Granulopenia.—The ambiguous expression 'leucopenia' has been avoided here. In using the term '*granulopenia*' it should be borne in mind that an absolute polymorphonuclear count which is granulopenic for one person is not necessarily granulopenic for another. The interpretation of the term must be related to the *pretherapy* normal count—hence the importance of this count for purposes of comparison subsequently. Thus, a patient with a normal high count of, say, 5000 polymorphs which drops to 1500 polymorphs is to be regarded more seriously than a patient with a low normal of, say, 3000 polymorphs which drops to 1500, the first representing a drop of 70 per cent and the second a drop of 50 per cent. In my opinion a mathematical definition of granulopenia, as so often attempted, is unwise and misleading. My own practice is temporarily to stop the antithyroid therapy in any patient in whom the blood-count shows *a drop of* 1000 *polymorphonuclears upon the pretherapy count*. Such a drop is evidence of marrow depression and is a granulopenia for the patient concerned. I appreciate that such an arbitrary figure is open to criticism, but I prefer to err on the side of caution.

Thiouracil Goitre.—High dosage, if prolonged, will produce a hyperplastic gland—a 'thiouracil goitre' (*Fig.* 26). (Riddell, 1953, 1954.) It is very undesirable that overdosage with antithyroid agent should occur. The resultant 'thiouracil goitre' may cause pressure symptoms and force surgery while the gland is still enlarged and vascular and so greatly increase the technical difficulties of the operation. Operation on a thiouracil goitre is an operation on an *arteriovenous fistula* (*Fig.* 27). Any arteriovenous fistula of sufficient magnitude will have an ill effect on the cardiac mechanism, and this is especially harmful in thyrotoxicosis. I have seen patients suffering from overdosage of antithyroid agent, and presenting with a huge, throbbing, vascular goitre, in whom the pulse-rate was rapid, although the patient was subthyroid. Leggett (1954) thinks that one element in such cases is the arteriovenous shunt in the vascular gland.

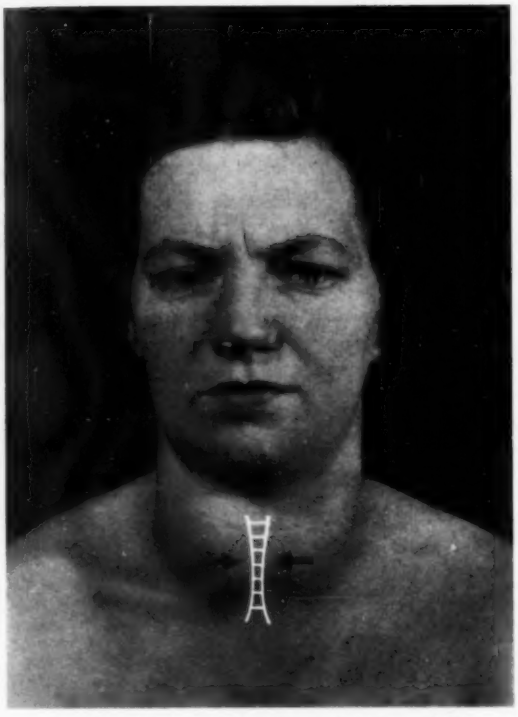


FIG. 26.—'*Thiouracil*' *goitre*, producing tracheal compression.

FIG. 27.—'*Thiouracil*' *goitre*: Bruit on auscultation (arteriovenous fistula).

Vocal Cord Thickening.—The thickening of the vocal cords (*Fig.* 28) which takes place when myxœdema is induced also constitutes a very real post-operative danger from œdema of the glottis, which may be serious enough to require tracheostomy. *Thyroidectomy is therefore strongly contra-indicated in the hypothyroid phase* and must be resisted unless it is forced upon the surgeon by increasing pressure symptoms. In these circumstances a very careful watch will be necessary post-operatively.

Myxœdema.—If myxœdema is produced by antithyroid agents an irreversible state may be set up, or at least a state which takes a long time to adjust itself (*Fig.* 29). If the patient is referred for surgery at this stage of overpreparation, a long delay must follow before operation can safely be undertaken—to allow the patient time to revert to a euthyroid state. In short, the net result of overtreatment—whether in the course of long- or short-term therapy—is seriously to slow up the patient's return to normal health and thyroid balance.

FIG. 28.—*Hypothyroidism* from overdosage with antithyroid agent. Laryngoscopy shows the swollen vocal cords with narrowing of the glottis. Subjectively there was a thick voice and inspiratory stridor.

A hypothyroid state can be avoided only by repeated examination of the patient throughout the period of administration of the antithyroid agent. If myxœdema or a goitre develop the treatment is to stop the drug as soon as the evidence of overdosage is detected.

Hæmorrhage.—Thiouracil produces effects upon the gland of primary toxic goitre which only occur minimally or not at all in the nodular thyroid of the older patient. It increases the size of the gland, renders its consistence hard and rigid, and so restricts its mobility at operation and increases its vascularity many times.

It is important to be aware of these effects, and be prepared for the very severe bleeding which can occur at operation. If this comes as a surprise it may well extend the most experienced surgeon. There is little doubt that isolated experiences of this kind, usually in insufficiently prepared glands, has done much to prejudice some surgeons against the antithyroid agents.

Much can be done to diminish the technical difficulties associated with the altered physical state of the gland (1) by careful preparation with iodine, (2) by avoiding pre-operative overdosage with thiouracil, and (3) by a sense of timing in the choice of the optimum moment for the operation; but despite observing these precautions there will still be occasional cases calling for all the operator's skill if bleeding is to be controlled, an adequate amount of gland removed, and no damage inflicted upon either of the recurrent laryngeal nerves.

A B

FIG. 29.—*Myxœdema following thiouracil therapy.* A, Before treatment; B, After treatment. Overdosage with antithyroid agent has produced a goitre and myxœdema, with thickening of the vocal cords.

Contra-indications to the Use of Antithyroid Agents.—

1. Patients with *mild thyrotoxicosis* (first degree) unless they have failed to respond to simpler remedies.

2. Patients with thyrotoxicosis of *intermediate severity* (second degree) who are to undergo *thyroidectomy*, as these patients can usually be brought to a safe operative level with iodine alone.

3. Patients with nodular goitre associated with *compression or deviation of the trachea* in whom the pressure symptoms might be aggravated by the administration of antithyroid agents (the same applies to patients with retrosternal or intrathoracic goitre).

4. Patients who are known to be *sensitive or resistant to, or to relapse* after taking, the antithyroid drugs. In these patients the continued administration of the drug may be unwise or simply ineffective.

5. Patients who are judged to be unsuitable for *long-term therapy*—the impatient, the unreliable, and those who are unwilling or unable to co-operate.

6. *Pregnancy*—an antithyroid agent should not be administered during the last four weeks of the pregnancy or while feeding the baby.

7. Toxic reaction—*with granulopenia*. The antithyroid agent should be abandoned immediately and permanently in all patients who develop a granulopenic toxic reaction.

8. Toxic reaction—*without granulopenia* (simple). If there is no evidence of marrow depression it is usually safe to continue treatment with an alternative antithyroid agent, but if a *second* simple reaction occurs it will generally be wise to abandon treatment with the agents at present available.

9. *Size*: If the goitre is already large it is likely to become larger with antithyroid treatment and to cause pressure symptoms.

THE MANAGEMENT OF THYROTOXICOSIS

(Excluding the use of radio-iodine, *see* p. 93)

The management of the thyrotoxic patient should be conducted in two distinct steps.

The first or *diagnostic* step is to determine the *form* of definitive treatment—medical (long-term) or surgical (short-term)—best suited to the individual concerned.

The second or *therapeutic* step is to apply the definitive treatment selected.

PART I.—THE FORM OF TREATMENT

Long- (Medical) or Short- (Surgical) Term Therapy?

When faced with a thyrotoxic patient, who may be young or old, who may be with or without enlargement of the thyroid gland, and with or without the classical features of the disease, it can be confusing to make up one's mind as to the most suitable definitive line of treatment. This is certainly not the occasion or the moment for an impulsive or hasty decision. The form treatment should take can only be concluded after reference to: (1) The severity of the thyrotoxicosis; (2) The clinical variety of the thyrotoxicosis.

1. The Severity of the Thyrotoxicosis.—There are varying degrees of severity of thyrotoxicosis. For the purpose of this communication the following entirely arbitrary divisions of thyrotoxicosis according to the *sleeping pulse-rate* are used.

1st degree thyrotoxicosis: Sleeping pulse-rate not raised above 90 (mild thyrotoxicosis).

2nd degree thyrotoxicosis: Sleeping pulse-rate between 90 and 110 (intermediate).

3rd degree thyrotoxicosis: Sleeping pulse-rate over 110 (severe thyrotoxicosis).

Clearly in so protean a disease so simple a classification is open to serious objection as there are other factors bearing upon the severity besides the pulse-rate; indeed any exaggerated feature such as severe loss of weight must be taken into consideration when assessing the degree of the thyrotoxicosis. The intention is to do no more than illustrate the advantage of including in publications a definition of the degree of thyrotoxicosis upon which treatment is based, as without this information comparisons are impossible. As tachycardia is the most constant (although not invariable) accompaniment of the disease, and the degree of its elevation an indication of its intensity, it has been chosen as the most reliable single measure for purposes of subdivision and comparison.

2. The Clinical Variety of the Thyrotoxicosis.—Clinically it will be found that patients when first seen can be placed in one or other of three groups:—

A *medical* group in whom there is present a special indication for medical treatment.

A *surgical* group in which there is present a special indication for surgical treatment.

An *indeterminate* group in which the method of treatment can only be decided after reviewing all the related factors.

MEDICAL GROUP

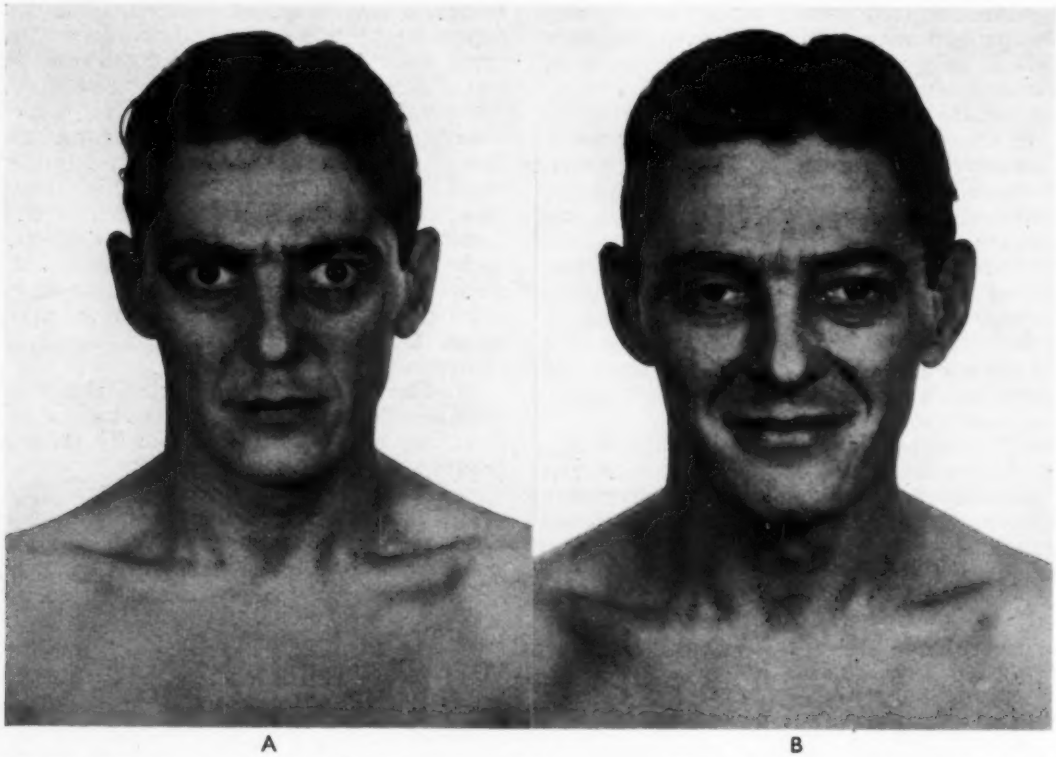
Indications for Medical Treatment

In arriving at a decision in an individual case I have found it helpful first to exclude those patients who for purposes of therapy fall naturally into the medical or surgical category.

Let us consider first those in whom medical treatment is indicated.

1. Mild Thyrotoxicosis (*Fig.* 30).—Medical treatment is indicated in all patients with mild thyrotoxicosis. The symptoms of mild thyrotoxicosis are not always easily discernible and their association with the thyroid is readily overlooked. They include lassitude, fine tremors of the fingers and tongue, a slight moisture of the palms, loss of weight, attacks of nervousness, and attacks of palpitation which are more readily provoked than is normal for the individual concerned, and a barely perceptible impression of a stare, together with a rise of the pulse-rate not exceeding 90 beats to the minute. *Surgery, the antithyroid drugs and iodine are alike contra-indicated.* Surgery is absolutely contra-indicated because it is unnecessary. The antithyroid drugs should not be used *in the first instance*, but only resorted to if rest and sedation fails. Iodine also has no place in the purely medical treatment of any form of thyrotoxicosis. "Iodine is to the thyrotoxic patient what morphia is to the 'acute abdomen'—it masks symptoms without curing the disease"—McEwan (1938). In the more severe cases it produces a rapid response which is misleading as the effect is only transient and is not maintained; but it may be significant enough to induce a false belief in non-surgical

measures, with the result that operative treatment is postponed unwisely (Keynes, 1935). If surgery is subsequently decided upon the response to the pre-operative course of iodine is prejudiced by the previous course, and will be nil unless a fallow interval of not less than six weeks is allowed before starting its readministration. Its use in the treatment of toxic goitre should therefore be restricted to the immediate pre-operative phase. " Iodine acts best on virgin soil " (Morley, 1936).



A B

FIG. 30.—*Mild thyrotoxicosis.* A, Before treatment; B, After treatment. The patient was treated conservatively: no iodine or antithyroid agent was used.

The danger with patients suffering from mild thyrotoxicosis is *overtreatment*. If such simple conservative measures as rest in bed, change of environment, and sedation are combined with sympathetic handling and the elimination of any causal factor, the majority of patients with mild thyrotoxicosis will with patience be able to be restored to whatever is their own normal thyroid balance. A very few only will require antithyroid agent in small dosage. The underlying constitutional disability is unaffected by treatment, so that the susceptibility to develop thyrotoxicosis remains—but the remission may be long and may be permanent.

Differential Diagnosis from Anxiety State.—Having said that the symptoms of thyrotoxicosis are readily overlooked, we will now take a contrary stand and say, with Mowat (1953), " the diagnosis of thyrotoxicosis is made all too frequently and on insufficient grounds ".

If the symptoms of an anxiety state are confused with and labelled as due to thyrotoxicosis an entirely wrong régime of treatment may be initiated. The points of resemblance—anxiety, fatigue, nervousness, loss of weight, tremor, and tachycardia—are numerous, so that it is to the points of difference that we must turn to make the differential diagnosis.

In the first place the personalities differ. The hyperthyroid patient is usually optimistic, cheerful, and anxious to get well; the patient with an anxiety state is tense, complaining, and inclined to self-pity. The hyperthyroid patient is energetic, but is easily tired out; the patient with an anxiety state is apathetic and tired all the time. The hyperthyroid patient has a warm hand and is intolerant to heat. The anxiety neurotic usually has a cold hand and is sensitive to cold. The pulse-rate is likely to be raised in both states, but it is more consistently raised in the thyrotoxic and during sleep, whereas in the anxiety state it is subject to fluctuations. In the hyperthyroid weight loss is usually associated with a normal or an increased appetite, while in the anxiety state there is a poor appetite frequently associated with indigestion and constipation or a spastic colon.

Borderline Cases.—If after considering these clinical points of difference the diagnosis remains obscure, it may be necessary to give a therapeutic trial course of iodine or antithyroid agents, or to resort to B.M.R., or radio-active iodine studies. These special investigations are, however, in practice not always as helpful and discriminating as might be expected. The shrewd and patient application of the clinical method is often more rewarding and discerning. In sorting out these borderline cases it must be remembered that while iodine has a specific action in lowering the raised basal rate in thyrotoxicosis it has no effect whatever on the basal rate

of normal healthy people. On the contrary, the antithyroid agents will not only lower the basal metabolism in cases of true thyrotoxicosis, but will cause a normal basal metabolism to fall even to a myxœdematous level, so that their administration as a diagnostic test in doubtful cases is of doubtful value. (Robertson, 1946.) The serum-creatine level, in conjunction with an accurate measurement of the sleeping pulse may be helpful (Freeman and Mattingly, 1956). The serum-creatine level (normal 0·6 mg. per 100 ml.) tends to be raised in hyperthyroidism (Griffiths, 1954), but the test is non-specific as it may also be raised in conditions associated with disordered muscle metabolism so that these must first be excluded.

2. **Masked Hyperthyroidism** (*Fig.* 31).—"There is no classical sign of thyrotoxicosis that may not be absent." Medical treatment is also the elective initial method in those thyrotoxic patients without a goitre and without eye signs—so called 'masked hyperthyroidism'. Most patients with masked hyperthyroidism are in the older age groups, and are particularly liable to present with cardiovascular symptoms (Towers, 1933), or loss of weight or muscular weakness. The size of the gland is no indication of the severity of the intoxication. In some of the most severe cases of thyrotoxicosis the thyroid gland is impalpable.

If the presenting symptom is associated with a goitre or exophthalmos—the diagnosis, though not necessarily the treatment, is straightforward, but if there is no goitre and there are no eye signs the association with the thyroid may be overlooked. The important matter is to bear thyrotoxicosis in mind when a patient presents with unexplained shortness of breath, loss of weight, or swelling of the ankles, unexplained sudden muscular weakness (Robertson, 1954; Brain, 1938), unexplained restlessness or diarrhœa, amenorrhœa or sterility, or, most significant of all, an *unexplained fibrillation.*

3. **Youth—Age—and Stress.**—Medical treatment should be employed whenever possible in young children and in the elderly and at times of exceptional physiological stress (Gardiner-Hill, 1928) such as puberty, pregnancy, and the menopause, when antithyroid cover will generally be all that is necessary.

Pregnancy.—

Antithyroid agents—and the mother: In the case of thyrotoxicosis associated with pregnancy "it is the thyrotoxicosis not the pregnancy which should be interrupted" (Rundle, 1951 a). With care it is possible to see most of these patients through their pregnancy without resort to operation. The dose of antithyroid agent should be regulated by and related to the clinical condition and not to the basal metabolic rate, which is raised in pregnancy (the rise averages 25 per cent above normal and occurs in the second half of the pregnancy). The smallest dose compatible with rendering the patient symptom-free should be employed. The maximum dosage during the last three months of treatment should not exceed 50 mg. propyl thiouracil twice daily (or the equivalent of other drugs), and in many instances a smaller dose will control the symptoms.

In those few cases in which the prospective mother does not tolerate the antithyroid agent, and in those cases in which pressure symptoms develop, thyroidectomy during pregnancy after iodine preparation may have to be carried out. It is unlikely that mis-carriage will occur, though possible. The thiouracils are secreted in the milk, so that if the thyrotoxicosis persists after parturition it is wise either to wean the child or to continue with only very small doses to avoid hypothyroidism in the baby.

Antithyroid agents—and the baby: No large series of abnormalities arising in the fœtus has ever been reported. One case is reported by Morris (1953),

FIG. 31.—*Masked hyperthyroidism.* This patient attended with an unexplained *fibrillation.* There was no goitre.

and 10 cases collected from the literature and 1 personal case were reported by Elphinstone (1953), but most of these referred back to the earlier period of the thiouracils when the dosage in pregnancy was not understood as it is to-day. On the other hand the birth of many normal infants following thiouracil treatment during pregnancy has been reported: Astwood (1951) 22 cases; MacGregor and Goodwin (1953) 15 cases; Fraser and Fisher (1953) 10 normal infants and 1 temporarily hypothyroid.

The danger of producing subthyroid babies as a result of antithyroid therapy during pregnancy, provided low dosage is used, appears to have been greatly exaggerated, but for safety iodine should replace the antithyroid agent for the last four weeks before delivery.

Precautions: Large quantities of *iodide* by the mouth during pregnancy for such conditions as asthma may cause enlargement of the fœtal thyroid, but can be safely taken in reduced dosage and this may be advisable in endemic goitrous areas.

Further pregnancy should be discouraged in all patients who have had thyrotoxicosis for at least a year after the thyrotoxicosis appears to be controlled.

4. Recurrent Post-operative Thyrotoxicosis (*Fig.* 32).—

Post-operative Assessment.—A careful investigation of patients with ' recurrent post-operative thyrotoxicosis ' can be revealing. It will be found that patients fall into two groups : (1) those with a genuine return of their toxic symptoms—*true* recurrent thyrotoxicosis—a minority in my experience, and (2) those in whom the toxic symptoms have been relieved but there is a persistence of an anxiety state—*false* recurrent thyrotoxicosis.

A B

FIG. 32.—*Recurrent thyrotoxicosis* (post-operative). A, Post-operative ; B, After treatment. The recurrence responded to antithyroid agent (propyl thiouracil).

In assessing recurrent thyrotoxicosis it is very easy to be misled by the symptoms of a *persisting anxiety state* and to treat such a patient mistakenly for a long period with antithyroid agent or even radio-iodine. For this reason it is wise to readmit all patients suspected of a recurrence of thyrotoxicosis and to reinvestigate them in exactly the same way as if they were presenting for the first time. It is not satisfactory to attempt a differential diagnosis in an out-patient department and it is a mistake to restart antithyroid treatment blindly.

The reassessment is not a prolonged affair—it can generally be completed within a week—and the time is well spent if it prevents an error in diagnosis and treatment.

The persistence post-operatively of an anxiety state generally indicates a failure in the process of selection for treatment. Patients with combined thyrotoxicosis and an anxiety state overlay are probably best stabilized by medical methods, but no treatment in this complex group is universally successful.

Treatment.—The treatment of recurrent thyrotoxicosis (unassociated with thyrotropic exophthalmos) is seldom the difficult or serious problem it used to be. There are three clinical varieties of post-operative recurrent thyrotoxicosis : (*a*) Those with no palpable thyroid tissue in the neck ; (*b*) Those with nodular regeneration of one or both lateral lobes ; and (*c*) Those with recurrence confined to the pyramidal lobe. The treatment differs.

a. No thyroid tissue palpable : Medical treatment has its cardinal and most valuable application in the treatment of those patients with post-operative recurrent thyrotoxicosis in whom there is no palpable regrowth of thyroid tissue. It is no exaggeration to say that the prognosis in these patients has been revolutionized by the advent of radio-iodine and the antithyroid agents. The decision as to which of these methods is used will be influenced by the age of the patient and by whether she is sensitive or not to the antithyroid drugs. *Surgery is absolutely contra-indicated.*

b. Thyroid tissue palpable : In these patients the recurrence is usually nodular in type. The choice as between surgery or medicine will be influenced by two considerations—the size of the thyroid recurrence and the integrity of the recurrent nerves. Re-operation on these patients is always hazardous because of the risk of damaging either or both inferior laryngeal nerves. If the recurrence is small, medical treatment with the antithyroid agents (or radio-iodine) is the method of choice. If the recurrence is bulky, surgery is to be preferred and should be carried out if laryngoscopy shows that both inferior laryngeal nerves are intact. If the recurrence is associated with an inferior laryngeal nerve palsy on the side opposite to the recurrence, re-operation incurs the risk of damaging the only remaining recurrent nerve so that an attempt should

be made to control the thyrotoxicosis with antithyroid agents. If the recurrence takes place on the same side as a nerve lesion, re-operation can be considered with less anxiety as the underlying nerve has already been damaged.

c. Pyramidal lobe recurrence : It is a simple matter to excise such a recurrence, and this should be done, but the local treatment may require supplementing with antithyroid therapy if the recurrence of toxic symptoms has been severe.

5. Malignant Exophthalmos (*Fig.* 33) (Pituitary Exophthalmos ; Thyrotropic Exophthalmos).—Medical treatment is advisable in the ophthalmic forms of thyrotoxicosis. It is important to assess the degree of thyrotoxicosis without regard to the eye signs and to treat the toxicity on its own merits. It may not be severe.

The term ' malignant ' is misleading and should be reserved for cases of proptosis in which the eyesight is threatened. The treatment of severe exophthalmos with or without ocular muscle paresis (ophthalmoplegia) remains unsatisfactory and unpredictable. There is strong experimental evidence that the exophthalmos is thyrotropic in origin and that the protrusion is due to œdema of the orbital contents, particularly of the orbital musculature (Rundle, Finlay-Jones, and Noad, 1953).

Both thyroidectomy and the antithyroid agents may increase the proptosis. If either is contemplated, and the issue may be forced because of the toxicity, thyroid extract should be administered at the same time in dosage as high as can be tolerated by the patient (in conjunction with antithyroid agent) with the intention of reducing the amount of thyrotropic hormone produced by the anterior lobe of the pituitary. Stilbœstrol may also depress thyrotropic output and may be given trial in doses of 10 mg. daily. Irradiation of the orbits and the pituitary gland has been used with indifferent results : X-rays are known to be capable of destroying lymphocytes and therefore might be expected to have some effect on the lymphocytic infiltration present in the orbital muscles. Hypophysectomy has also been tried. The use of cortisone and corticotrophin (ACTH) has been reported upon by a Medical Research Council panel (1955), in whose series results generally were discouraging, but the suggestion is made that cortisone is worthy of further trial in really acute cases.

Orbital decompression by the method of Naffzigger (1954), whereby the orbit is unroofed, will be necessary in progressive cases to save the sight. A temporary tarsorrhaphy may usefully be combined with the decompression. *Tarsorrhaphy* should be carried out *early* in severe proptosis. It is often recommended too late, when corneal ulceration, hypopyon, and other ocular complications have developed.

6. Plump Type.—There is no convincing evidence that the overweight patient with thyrotoxicosis should be segregated into a special clinical group. Appetite is specifically influenced by thyrotoxicosis, and the patient, in an attempt to counteract the nutritional effects of her increased metabolism, may overcompensate by overeating and so put on weight.

The well-nourished appearance of the plump patients is deceptive and it has to be remembered that they may be no less severely ill than more typical cases with an equivalent degree of thyrotoxicosis. There is no specific contra-indication to surgery in these cases, and they are only discussed here for convenience. They should be selected for medical or surgical treatment according to the criteria laid down for patients in the ' indeterminate ' group.

FIG. 33.—*Ophthalmoplegia* affecting the right superior rectus muscle associated with mild thyrotoxicosis.

There is no doubt, however, that thyrotoxic patients who are fat are *not* easy patients to maintain in a euthyroid state over a 2–3 year period, for further weight increase is difficult to prevent with antithyroid therapy, despite carbohydrate restriction of diet.

7. Poor Operative Risks.—Finally medical treatment is indicated in poor operative risks and when expert surgery is unavailable or refused.

SURGICAL GROUP

INDICATIONS FOR SURGICAL TREATMENT

Surgery, as the primary definitive line of treatment, is indicated in the following circumstances :—

1. Pressure Symptoms.—When pressure symptoms are present or when symptoms of pressure might be precipitated by the use of antithyroid agent as in a retrosternal or intrathoracic goitre (*Fig.* 34), although toxic change in the latter is exceedingly rare. The pressure symptoms vary from a sense of pressure in the neck to choking sensations or even a feeling of suffocation in more severe cases. In non-malignant goitres dysphagia is strangely rare even when the œsophagus is grossly displaced. A chronic cough, hoarseness of the voice, and inspiratory stridor may be a direct pressure effect, but in all these cases involvement of the recurrent nerves should be excluded by laryngoscopy. Displacement or compression of the trachea as shown by radiography will also contra-indicate the use of antithryoid agents and be an indication for thyroidectomy.

2. Toxic Nodular Goitre.—Thyroidectomy is indicated in the treatment of toxic nodular goitre—with a few exceptions. If the toxic nodular goitre

is unilateral (toxic adenoma) the treatment is surgical at all ages. If the toxic nodular goitre is bilateral and there is marked enlargement of both lobes the treatment is again surgical.

If the patient is middle-aged or elderly and the nodularity amounts to no more than a smooth asymmetry in ' size ' of the two lateral lobes, good results can be obtained in carefully selected cases from

FIG. 34.—*Toxic nodular goitre* with retrosternal extension: the use of antithyroid agent is dangerous as by increasing the size of the goitre it may precipitate acute pressure symptoms.

medical treatment only (see menopausal and post-menopausal group), as concomitant malignant change is very rare.

3. Failed Medical Treatment.—By a process of elimination thyroidectomy or radio-active iodine becomes the only effective expedient in those patients in whom medical treatment with antithyroid drugs has failed, i.e., the thiouracil sensitive, the thiouracil relapses, and the thiouracil resistant.

4. Social and Economic.—Thyroidectomy may also be the most desirable method of treatment in those who are unable or unwilling to attend regularly, in the unreliable and unco-operative patient, or for social or economic reasons.

5. Malignancy.—Surgical treatment is indicated if malignancy cannot be excluded.

6. Size.—Size alone can be a contra-indication to medical treatment. A large goitre often becomes even larger with antithyroid treatment, and even if it does not cause pressure symptoms requiring surgical intervention, its presence is uncomfortable and is at meal times a constant reminder of the patient's disability. The cosmetic appearance is unsightly and if the patient is a male he is likely to have to buy new shirts and collars.

7. The Thyrocardiac Patient.*—The treatment of ' thyrocardiac ' patients presents a special problem; although not all cases are treated surgically it is convenient to consider the group as a whole at this stage. Their management and their prognosis has changed, and changed to their advantage, as a result of the advent of the antithyroid drugs and radio-iodine.

Incidence of Thyrotoxic Fibrillation.—Thyrotoxicosis is not as common a cause of auricular fibrillation as may be supposed, but it is by far the most susceptible to successful treatment. The commonest cause of auricular fibrillation is rheumatic heart disease (34·4 per cent), followed by coronary artery disease (31·1 per cent), hypertension (16·9 per cent), with thyrotoxicosis as an aetiological factor in only 7·5 per cent of 575 cases of fibrillation (McEachern and Baker, 1932). Other writers have found thyrotoxicosis responsible in 14 per cent of 200 cases (Parkinson and Campbell, 1930) and 4 per cent of 376 cases (White and Jones, 1928). The number of patients with thyrotoxicosis developing auricular fibrillation is, however, considerable. Papp (1945) says that 20 per cent of all patients with toxic goitre develop this symptom and that 80 per cent of all thyrotoxic patients over the age of 60 fibrillate. The fibrillation at first is paroxysmal, but later becomes established, and this is the forerunner of congestive heart failure. Once this stage of injury to the heart has been reached life is endangered. It is interesting to note that Lange (1953) found the incidence of cardiac involvement to be twice as common in males as in females.

The Antithyroid Agents and Thyrotoxic Fibrillation.—In one-third to one-half of cases of auricular fibrillation of thyrotoxic origin, the heart reverts spontaneously to normal rhythm following the administration of thiouracil or its derivatives only. The return of normal rhythm was reported in 12 out of 18 cases (67 per cent) by McGarack, Gerl, Morton, Vogel, and Schwimmer (1945); in 8 out of 16 cases (50 per cent) by Cookson and Staines (1947); in 8 out of 15 (53 per cent) by Murray (1950); in 4 out of 10 (40 per cent) by Verel (1949); in 12 out of 28 cases (43 per cent) by Goodwin (1949); and in 9 out of 23 cases (39 per cent) by Douglas and Kennie (1952). Return to normal rhythm may infrequently be associated with peripheral embolism and 4 such experiences are reported by Aird (1949).

The decision to use antithyroid agent should depend upon the severity of the thyrotoxicosis *and not* the fibrillation. The fact that normal rhythm is frequently restored during the course of the administration of an antithyroid agent has wrongly shifted the emphasis of the purpose of using antithyroid agent, which is primarily to control the thyrotoxicosis and not the fibrillation, for which there are other well-established remedies available.

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* Exception may be taken to the compound word *thyrocardiac* but at least it is etymologically correct: θυρεοειδης, 'shield shaped', καρδια 'heart'. But *goitrogenic*, though a useful adjective, is a hybrid of the worst type, being compounded of the Latin 'guttur', throat, or French 'goitre' and the Greek suffix γενης and I take no responsibility for its introduction to the vocabulary of thyroid diseases.

Treatment of the Thyrocardiac Patient

There are certain special features that need to be taken into consideration in deciding the treatment of patients with thyrotoxic fibrillation. In the first place there is a double lesion to treat, the thyrotoxicosis and the fibrillation, and it is important that the severity of each of these conditions should be separately assessed.

The Assessment of the Thyrotoxicosis.—It is perhaps not sufficiently well known that while the thyrotoxicosis may be severe it is much more commonly relatively mild or at most of moderate severity only. The problem in fact is usually more ' cardiac ' than thyrotoxic. This point is made because the practice has grown up of giving antithyroid agent to all patients with thyrotoxic fibrillation : if the patient is to be treated medically this is reasonable, but if the patient is being prepared for operation and the thyrotoxicosis is not severe, the use of iodine is all that is necessary to bring the patient to a safe operative level. The pre-operative use of antithyroid agent in all cases merely adds difficulty without adding safety to the operation. If the thyrotoxicosis is severe, antithyroid agent will be necessary in its usual dosage. The pre-operative antithyroid treatment in thyrocardiac patients should be carried up to and beyond the point when one judges that the thyrotoxicosis is controlled. This is contrary to the practice advised in the pre-operative preparation of the majority of patients without cardiovascular complications, who should be operated upon as soon as stabilization has been effected ; but the thyrocardiac benefits from a further *brief* period of rehabilitation in which to consolidate his or her clinical improvement. The antithyroid agent should therefore be prolonged in reduced dosage and in combination with iodine for approximately two weeks after the thyrotoxicosis has been controlled before operation is carried out.

The Assessment of the Auricular Fibrillation.—This should be related to the duration of the thyrotoxicosis, the rate of the fibrillation, and the degree of cardiac damage. In a long-standing case of untreated thyrotoxicosis the heart may be greatly enlarged, as shown on radiography, and other characteristics of heart failure may be present. In such a case the treatment of the cardiac condition becomes the dominating consideration. In cases of recent origin, however, no special treatment of the fibrillation *per se* is likely to be necessary. A patient with slow fibrillation can safely be operated upon—provided there is no cardiac failure—as soon as the toxicity has been controlled. It is certainly not an essential feature of the pre-operative preparation that the fibrillation should be abolished before operation can be undertaken. In short, the management depends not so much upon the restoration of normal rhythm as upon whether the fibrillation is satisfactorily *compensated or not.*

a. The fibrillation is compensated : If there is no heart failure a fibrillation with a ventricular rate of 100 or less should not contra-indicate surgical measures and thyroidectomy can safely be carried out provided the toxic goitre has been converted into a non-toxic goitre.

b. The fibrillation is not compensated (bad-risk cases) : If the patient is in failure or the auricular fibrillation is rapid, the use of digitalis will have to be considered. (Digitalis, of course, should never be given for cases of simple tachycardia.) Thyrotoxic patients are particularly resistant to digitalis and respond poorly to it. The dosage, which is likely to be higher than that usually employed, and duration of treatment with digitalis should be controlled by a physician. If the heart failure remains unrelieved, although the thyrotoxicosis is controlled, surgery will have to be postponed indefinitely. *Radio-iodine* should be considered at an early stage in the treatment of patients who respond unsatisfactorily to the antithyroid agents, and may be of especial value, sometimes in combination with antithyroid agent, in the treatment of the advanced and feeble thyrocardiac with congestive failure.

Post-operative Fibrillation.—Post-operatively a return to normal rhythm is usual but if the fibrillation persists both digitalis, in reduced doses, and iodine should be kept up for one week. Some physicians advise that digitalis should not be given post-operatively to fibrillators as it encourages ectopic rhythms, and may perpetuate a persistent fibrillation. A contrary view is that digitalis should be administered to these patients in the belief that the risk of perpetuating the fibrillation is less than the risk of heart failure developing, due to a post-operative rapid uncontrolled fibrillation. If the fibrillation has not disappeared by the fifth day after the thyroidectomy, quinidine is the drug of choice and should be given in divided and increasing doses (Papp, 1945) in association with anticoagulants to prevent embolism. It is powerful and, though it can be toxic, it may be given in high dosage safely over a short period, as it is rapidly excreted.

Choice of Treatment.—My own opinion is that the treatment of choice for thyrotoxic fibrillation in the good-risk case remains surgical after suitable preparation. In the bad-risk case the thyrotoxicosis should be controlled by antithyroid agent or radio-iodine or both, and the heart condition should be treated with digitalis or quinidine and such other medical and nursing methods as are deemed appropriate. In short, while this means that thyrotoxic fibrillation is no longer the absolute indication for surgery that it was in the past, surgery remains the most effective method of treatment in all except the frail, the elderly, and those in whom the cardiac failure cannot be rectified.

INDETERMINATE GROUP

The exclusion of those patients who by general consent fall naturally for treatment into a medical or surgical category leaves us with a large residual group—the largest group of all—for consideration. It is the group of patients with primary thyrotoxicosis of second or third degree. Here the enlargement of the gland is smooth and symmetrical. It is concerning these patients, some young, some middle-aged, some elderly, that the difference of opinion exists as to whether their treatment should be directed along medical or surgical lines. The controversy was sharpest in the early days following the introduction of thiouracil, when exaggerated claims were made for the permanence of its stabilizing effect which have not subsequently been substantiated.

Experience has now shown that we shall be wrong if we treat all these patients by either method exclusively. If we treat all patients in this group surgically then we shall automatically operate upon a number who might have been stabilized medically. If we treat all patients in this group medically we are going to submit a considerable proportion to a prolonged and eventually fruitless course of therapy. Nevertheless it is argued by some that all these patients in the first instance should be treated

A B

FIG. 35.—'*Short-term*' *therapy* with antithyroid agent. A, Before thyroidectomy; B, After thyroidectomy. Younger age group; diffuse toxic goitre: third degree. If this patient had had *second* degree thyrotoxicosis she could have been brought to a safe operative level with *iodine* alone.

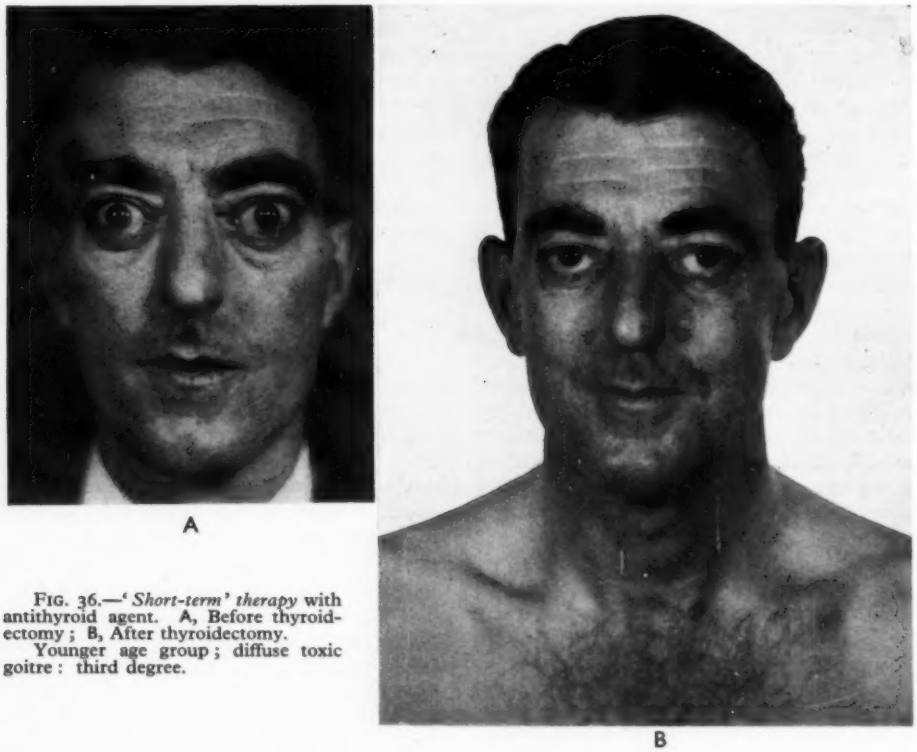

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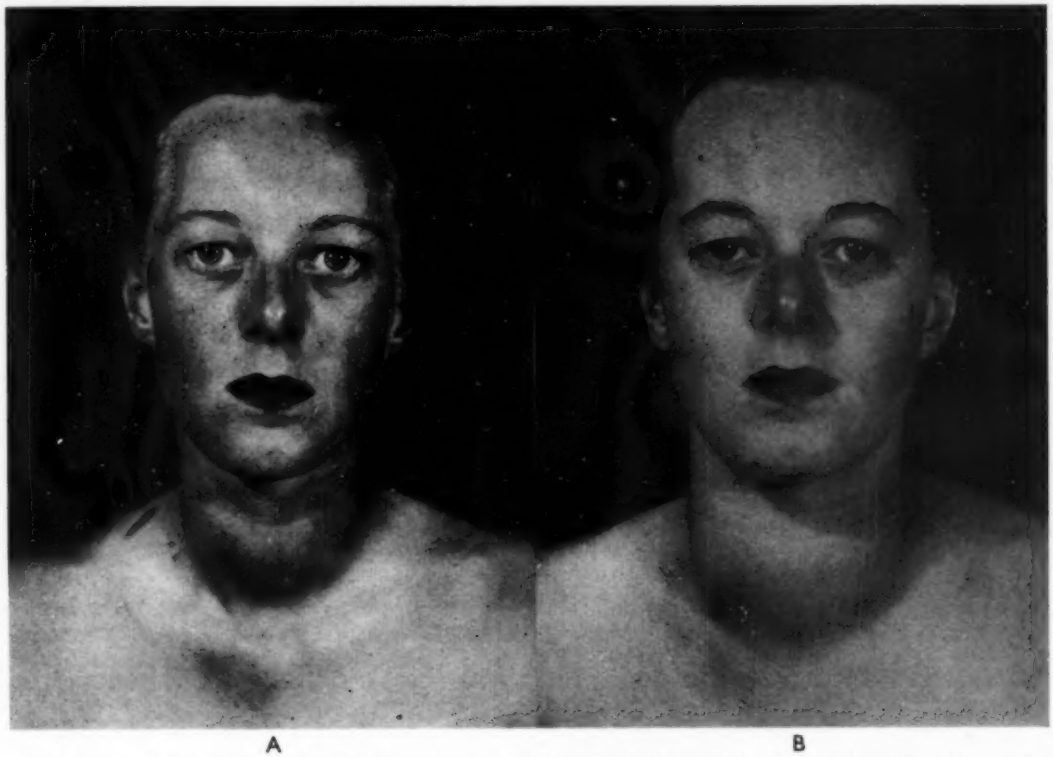
FIG. 36.—'*Short-term*' *therapy* with antithyroid agent. A, Before thyroidectomy; B, After thyroidectomy.
Younger age group; diffuse toxic goitre: third degree.

medically and that only those who relapse following treatment should be passed to surgery. This is an attitude which fails to take into consideration the varying demands of the different age groups. Thoughtful surgeons operating upon the thyroid to-day are fully aware of the value of the antithyroid agents and give them full scope, but at the same time feel that certain patients in this group should be operated upon just as some others should be encouraged to continue with antithyroid therapy only. There is a place for both methods of treatment.



A B

FIG. 37.—A, Before treatment; B, After treatment. To illustrate the *hyperplastic* response to antithyroid agent in a girl aged 19. This type of gland is very vascular.

The decision between the two forms of treatment can usually be resolved by reference to a number of points, which I will call the four factors—these are :—

The patient's age;
The patient's attitude;
The facilities available;
The precipitating agent.

Of these the determining factor is the patient's *age*.

Age.—

Younger Age Group (*Premenopause, aged* 18 *to* 40) (*Figs.* 35, 36).—Broadly speaking, adult patients developing second- or third-degree thyrotoxicosis any time before the menopause should be operated upon unless there is a contra-indication. The disappointing long-term results of antithyroid-therapy have produced a swing of the pendulum back towards surgical treatment, particularly for the younger *adult* patients. There is a natural reluctance to interfere surgically with the endocrine system at any age, yet younger patients (excluding children and adolescents) do not tolerate well the tedium of prolonged antithyroid therapy. They are impatient of results and inclined to find the repeated visits to hospital tedious and continuous tablet medication irksome, and for these reasons they may not progress favourably. More important still, those in the younger age group —because the gland reacts maximally to the antithyroid agent (*Fig.* 37)—are more liable to develop a thiouracil goitre and quite suddenly slip over into myxœdema unless very frequent and time-consuming visits are made to hospital or practitioner for reassessment and supervision. For these reasons in the premenopausal group, certainly in those under 40, it has been my experience that better results can be achieved by thyroidectomy than by purely medical methods of treatment. The fact that there will be patients who refuse surgery or are unsuited to it does not invalidate the argument or the experience upon which it is based.

Older Age Group (*Menopausal and Postmenopausal*) (*Figs.* 38, 39).—In the older patients, for exactly the opposite reasons to those just set down, there should be an inclination towards medical treatment as the initial method of choice. In these patients there is a less vigorous overall response by the gland and in consequence less likelihood of the development of a thiouracil goitre or myxœdema: in addition, older patients are usually more tolerantly inclined than their daughters towards this slower method of stabilization.

In patients of *menopausal* age, therefore, who are responding well it will be wise to try to avoid thyroidectomy by giving antithyroid agents a fair trial. Commonly a thyrotoxic flare-up during the menopause is a transient manifestation of the disease and will die down as the climacteric comes naturally to its end.

Similarly *postmenopausal* patients tend to respond in a more satisfactory and lasting manner to long-term treatment by antithyroid agents than patients in the younger age group. They should therefore also be encouraged provided they tolerate the drug well, to persist with the full course of antithyroid

A B

FIG. 38.—*'Long-term' therapy.* A, Before antithyroid agent; Middle-aged group (menopausal); diffuse toxic goitre. B, After antithyroid agent.

A B

FIG. 39.— *Long-term' therapy.* A, Before antithyroid agent; B, After antithyroid agent. Elderly group (postmenopausal); diffuse toxic goitre. This patient presented with a history of losing 3 st. in weight.

agent and the subsequent maintenance dose. If such a course is followed by a relapse then surgery can be considered.

Thyroidectomy will, however, continue to be the method of choice in this group for cases of established toxic *nodular* goitre and for all cases in which long-term therapy or radio-iodine seems likely to be unsuited to the patient in question.

Asymmetry of the Thyroid.—While the foregoing remarks apply essentially to patients with the smooth, uniform enlargement of primary thyrotoxicosis, it has to be borne in mind that this form of the disease diminishes in frequency with advancing age and after the menopause nodularity of the gland is more commonly seen than smoothness. In my view cases of toxic nodular goitre in which the nodularity amounts to no more than a slight dissimilarity in the size of the two lobes, as opposed to bossing of the surface, should in the first instance be given the opportunity of stabilization by antithyroid agents, as these patients also may respond well to medical treatment. Naturally this will not be contemplated if there is any suspicion of malignancy, but this is improbable in the type of gland described. Even in the coarsely nodular form of toxic goitre the coexistence of thyrotoxicosis and malignancy is exceedingly rare.

Apart from the patient's age the decision as to whether the treatment should be along medical or surgical lines will be influenced by the patient's preference, the presence or absence of a causal agent, and by the facilities available.

The Patient's Preference.—Patients with thyrotoxicosis are usually intelligent and their own wishes in regard to treatment must be consulted. The advantages and disadvantages of both methods should be explained to them. For example, the surgical cure is quick and permanent and removes the goitre, but involves an operation with its attendant mortality and morbidity, both of which are higher than that following the antithyroid drugs; medical treatment may produce relief of symptoms without an operation but a permanent cure is not certain and surgery may be necessary in the end. The time lost away from work is not substantially different as between the two methods, for although operation involves a continuous period away for a short time, long-term therapy involves repeated absences over a protracted period. An unmarried girl with an unsightly goitre, a young man or woman about to get married, a mother with a young family or a father with a small private business, are likely to elect for surgery, whereas an elderly patient may be less influenced by cosmetic considerations or urgency and prefer medical treatment. Some patients find medical treatment tedious and frustrating, others will show improvement only when told the surgery is not contemplated—and so on.

Facilities Available.—If the surgical facilities available are poor, as they can be, it will be prudent to continue with medical treatment. Only if they are good does surgery become an alternative to medical methods. A slow response and a lifetime with antithyroid agent is to be preferred to a quick response and a lifetime with both recurrent laryngeal nerves paralysed.

The medical facilities available can also be poor—by this I mean the time and care the physician concerned is prepared or able to give to the patient.

The Precipitating Factor.—Is there a causal agent? It is typical of the contrariness of thyrotoxicosis that in more than half the patients no convincing precipitating factor can be found. Nevertheless gentle questioning is worthwhile and in a few a causal agent—the spark that may have ignited the fire—is found. If such a factor is revealed and can be removed or adjusted the patient will be more than halfway towards a permanent relief of symptoms without any other form of treatment.

Causal agent present: In searching for a causal agent it should first be established that the patient is not passing through one of the normal periods of excessive *physiological* demand—by this I mean puberty, pregnancy, childbirth, or the menopause, for each of these states may so alter the potential thyrotoxic patient's delicately preserved physical and mental balance as to turn the scales and precipitate an attack of thyrotoxicosis. *Intercurrent* illness, infection or disease should next be excluded. A thorough general clinical examination is always advisable or some minor organic lesion such as an innocent lump in the breast, its significance magnified in the patient's eyes and about which she has not had the courage to seek advice, may remain undisclosed and unrevealed. Special inquiry should then be made in privacy and tactfully into the question of emotional stress. In my experience the most frequent contributing factors are housing difficulties often associated with living with 'in-laws'; exhaustion from the prolonged strain of overwork in the home or nursing a sick relative; bereavement from the death of a close friend or member of the family; an unsuitable occupation; or financial or domestic worries in their manifold varieties. A holiday or change of employment, or time alone, will put some, but not all, of these matters right.

It is in the cases in which there is an obvious domestic or psychological obstacle to recovery which *cannot be removed* by such simple measures, such as an incompatible marriage partner, when the greatest judgement is required in determining the most suitable form of treatment. Such patients will almost certainly relapse if treated with antithyroid agent alone. In the same way operation is likely to be only partially successful. Nevertheless in these particular circumstances the possibility of surgery should not be altogether excluded from our deliberations. A subtotal thyroidectomy upon a severely thyrotoxic patient in this category (after suitable preparation) may result in so significant an improvement in their physical state as to enable them to review and reassess their own problems with a fresh outlook and in a more balanced manner. No rules, however, can be laid down. Each patient and each problem must be assessed separately and treated individually.

Causal agent absent: If no precipitating factor can be found, and this is more often the case than not, the patient must be treated according to the degree of thyrotoxicosis present.

PART II.—DEFINITIVE TREATMENT

The *definitive* treatment is determined by the clinical variety of the thyrotoxicosis and the degree

of thyroidin toxication present (p. 33). The steps that remain to be taken before reaching this final phase will now be discussed.

General Management

In Bed.—The initial management of all patients whether they are destined for medical or surgical treatment is the same. The patient is admitted for a period of observation and investigation. The actual process of admission itself should be made as personal as possible. It requires considerable courage to go to hospital at all and a casual or unkindly initial reception can prejudice the issue from the start. Admission is advised as it is generally not possible in the brief and sometimes hurried encounter which takes place at the first attendance in an out-patient department or consulting room to make a correct assessment of the degree of thyrotoxicosis. The period need only be brief, but it is necessary. It is used by the clinician to study his patient with a view to coming to a conclusion as to the best line of treatment to adopt. This is not always an easy matter. Although the long periods of rest in bed which were so usual in the prethiouracil days are much less often required to-day, it is unwise in the case of the more ill patients to hurry them home too soon. While continuous recumbency is by no means necessary—after the first few days of the resting phase most-patients should be allowed to go to the bathroom and to get up for a short time each evening—rest and *relaxation* in bed in an atmosphere of reassurance and optimism still has a therapeutic value. *It is a mistake to drive thyrotoxic patients to recovery too fast.*

Toxic goitre patients do very well in a general surgical ward where they may with advantage be located together as a small special unit within a larger general one. They see other patients with the same malady getting up and getting better, they see one another before and after the operation, and the patients who have had their operation can exhibit their scars and generally improve the confidence of those whose ordeal still lies before them. A special ward reserved for goitre cases only is not necessary or in my opinion desirable. Occasionally a very toxic and restless patient should be put into a single room to avoid distressing others, but should not be kept apart longer than is necessary.

Sedation.—It is a good rule that all patients should be fully sedated on their first night in hospital. When the patient has settled down there is usually little difficulty in getting to sleep at night. If any difficulty is encountered, chloral gr. 30 may be used for this purpose. Nervousness and restlessness during the day will require to be controlled in the majority of cases. The best drug to use here is sodium phenobarbitone (luminal) in doses of gr. ½ two or three times a day, or sodium amytal gr. ¾–1½ t.d.s. In the more severe cases it may be necessary to increase the dosage of luminal, or even to give it by injection in its soluble form. For the most severe cases one of the opium derivatives may be needed, and the opium pill can be a very useful drug in these cases.

Diet.—A generous well-balanced *high-calorie* diet, unrestricted in variety, with extra milk feeds and malt is important for these patients, and the carbohydrate content should be relatively high, as the organs in thyrotoxicosis may become depleted of their glycogen stores. The problem of nutrition in the hyperthyroid patient is, however, not solely that of providing a diet of adequate caloric content. It is now well known that the hyperthyroid state is often associated with deficiency of *vitamin B* (both B_1 and B complex). (Mason and Zintel, 1946.) Thyrotoxic patients use more thiamine; they waste more and store less in the liver. Furthermore the resemblance of the symptoms of vitamin-B deficiency such as palpitations, dyspnœa, and fatigue, to the major cardiovascular symptoms of thyrotoxicosis are, to say the least of it, striking (Means, Hertz, and Lerman, 1937). For these reasons an adequate supply of vitamin B should be included in the diet. Increased *fluid* intake is also necessary because of increased protein catabolism, urea formation, creatinuria, and polyuria, which are usual in cases of toxic goitre.

Out of Bed.—In-patient treatment can give way to out-patient treatment as soon as the patient seems well and strong enough to make the necessary journeys to attend regularly. '*Short-term*' patients being prepared for surgery may with safety and advantage receive the greater part of their preoperative preparation—both antithyroid agent and iodine—in their own homes provided the home surroundings are satisfactory and that they attend at weekly intervals for supervision and reassessment.

'*Long-term*' patients need rather different handling; some will only make progress if allowed to return home as soon as possible—others will only do so if separated from their environment, and for these convalescence should be arranged. Once they are symptom-free they should be allowed to return to work. The reluctant should be encouraged to do so or they will lose confidence in their ability to pick up where they left off; the enthusiastic should be allowed to do so as they need the interest of employment to keep them well. All patients on long-term therapy should keep a weekly record of their bodyweight and should attend their practitioner or hospital at weekly intervals at first, though this period can be lengthened as the course proceeds.

Preliminary Investigations.—

General.—The preliminary investigations are carried out after admission and with the patient at rest in bed. They include a general clinical examination, a record of the sleeping pulse-rate, a 'baseline' differential white blood-count—an initial pretherapy white-cell count below 3000 associated with neutropenia contra-indicates treatment with antithyroid agent—and a B.M.R. The weight is also taken, the neck measured and radiographed to exclude deviation or compression of the trachea or retrosternal goitre, the vocal cords inspected by laryngoscopy in operation cases (*Fig.* 40) (Riddell, 1953), and cardiological and other opinions obtained when in doubt. All toxic patients should, in addition, be interviewed by a mature and sympathetic almoner, and in exceptional cases by a psychiatrist, so that we may be familiar with the home housing conditions and other relevant social and personal factors.

A *septic focus*, if found, does not necessarily require eradication before thyroidectomy can be

contemplated. In my view the *treatment of the thyrotoxicosis should take priority* over the treatment of any subsidiary lesion unless it is serious. It is insufficiently appreciated that tonsillectomy and similar minor operations, in the uncontrolled thyrotoxic subject, carry nearly the same risk of post-operative thyroid crisis and death as the major operation on the thyroid gland itself (Dunlop, Davidson, and McNee, 1953). If extensive dental extractions or tonsillectomy are envisaged it is better for the patient to postpone these operations rather than the thyroidectomy, but if they must be undertaken the thyrotoxicosis should first be controlled by a pre-operative course of antithyroid agent. If some more urgent condition such as an abscess or acute appendicitis arises during the course of treatment, neomercazole has the advantage that it will hold the thyrotoxicosis in check until such matters are attended to. But *delays and interruptions* in reaching the main objective —the thyroidectomy—should be avoided as far as is safe and reasonable.

Special Tests.—

1. *Basal metabolic rate* : It is well to acquaint the patient with the purpose and general conduct of the basal metabolism test (Robertson, 1946) beforehand so that the strangeness of the procedure may not disturb her. The *basal metabolic rate* should be interpreted with caution and only after relating it to the *clinical* findings. It is not an out-patient test. It is not a panacea, but if it is accurately determined it can be useful. It is most accurate in the hypothyroid states. I have found it of particular value in assessing the degree of post-operative recurrent thyrotoxicosis and myxœdema, and as a check in the course of long-term antithyroid therapy. It may also be of value in masked hyperthyroidism and in gathering evidence in difficult borderline cases. Widely differing results obtained on consecutive days should lead the clinician to suspect that the test has been performed with insufficient technical skill or under non-basal conditions rather than to regard it as valueless. False positives with high readings are most prone to occur in the anxious and apprehensive, in whom basal conditions are more difficult to ensure. False positives can normally be eliminated by the preliminary administration of a sedative such as sodium amytal or nembutal (Dynes, 1949), and by carrying out the test as an in-patient and in an atmosphere conducive to mental and bodily rest. If two readings are presented for interpretation, the inclination should be to choose the lower reading as being likely to be more reliable.

2. *Serum-cholesterol level* (*normal* 100 *to* 230 *mg. per cent*) :—This may be unaltered in hyperthyroidism and is of little value in determining the degree of thyrotoxicosis. There is no support for the theory that in hyperthyroidism the blood-cholesterol is inversely proportional to the metabolic rate. But in hypothyroid states there does appear to be some such relationship and the serum-cholesterol may be considerably elevated and so be a valuable guide in assessing the degree of myxœdema present (Gardner and Gainsborough, 1928). The reason for the raised level is not fully understood. The serum protein-bound iodine, serum-creatine (Griffiths, 1951), and radio-iodine clearance tests are not necessary as routine estimations, but may be helpful in exceptional cases. All are invalidated by the previous administration of iodine.

Surgical or Medical Treatment?—The evidence required for this final decision is now complete. The degree and clinical variety of the thyrotoxicosis is known. The choice between short- and long-term therapy can now be made. Thereafter, it only remains to apply the treatment selected. The surgical (short-term) is taken first.

FIG. 40.—*Recurrent thyrotoxicosis* (two previous operations). Laryngoscopy revealed a paralysed vocal cord. Further surgery is absolutely contra-indicated. The patient was treated with antithyroid agent.

SHORT-TERM THERAPY—SURGICAL TREATMENT

When we speak of the surgical treatment of thyrotoxicosis we infer treatment by combined medicine and surgery. Operation is only the culminating act in the final phase of a combined procedure. The pre-operative preparation of patients with second- and third-degree thyrotoxicosis differs.

Pre-operative Preparation for Second-degree Thyrotoxicosis (Sleeping pulse 90–110).—Patients with thyrotoxicosis of intermediate severity can be brought, with a few exceptions, to a safe operative level with *iodine* alone. Many fall into this category. It is necessary to stress this fact because in recent years there has been a tendency to advise the use of antithyroid agents—"just for safety"—in the preparation of all patients undergoing thyroidectomy for toxic goitre regardless of the initial severity of the disease. As a generalization this is misleading and unsound. Antithyroid agents should essentially be reserved for the

pre-operative preparation of patients with *severe* thyrotoxicosis (third degree).

Toxic Nodular Goitre.—The pre-operative preparation of patients with toxic nodular goitre, whether unilateral or bilateral, is similar—that is, with iodine only or with antithyroid agent followed by iodine, according to the severity of the thyrotoxicosis. There is no reason to withhold antithyroid agent in the pre-operative preparation of patients with toxic nodular goitre unassociated with pressure symptoms, provided it is administered under close supervision and followed by iodine in the usual way. The response to antithyroid agent in this group is somewhat slower than with the toxic diffuse type.

Pre-operative iodine: It is simply a matter of individual preference as to the form in which the iodine is prescribed. It is said that a soup made from seaweed was employed by the Chinese in the treatment of goitre many centuries before Christ, and certainly burnt sponge has been used since the middle of the eighteenth century. It is, however, more usual to-day to give the iodine in aqueous solution as Lugol's iodine (5 per cent iodine, 10 per cent potassium iodide in water), min. 10 t.d.s. in milk, although all *soluble* compounds of iodine are equally effective (Robertson, 1946) and sodium and potassium iodide particularly more efficient. Potassium iodide, gr. 4½ or sodium iodide gr. 4 are equivalent to 30 min. of Lugol's solution. Dosage in excess of this is valueless as the excess iodine is not utilized by the gland. The practice of giving gradually increasing doses has no advantage and is only confusing to dispenser and patient alike; a *constant daily dose* should be given.

Operation is carried out at the moment of minimum risk, that is when the maximum lowering of the pulse-rate has been obtained. This is usually 10 days after starting the course, but as this point may be reached earlier, e.g., 8th day, or later, e.g., 12th day, no rule of thumb should be followed or some cases will be operated upon prematurely and others after the iodine effect has begun to wear off. If the iodine is continued too long another effect becomes apparent. The gland becomes hard, and this increases the difficulties of its manipulation during the operation of thyroidectomy.

Post-operative iodine: Should iodine be administered after the operation? The answer is that no harm comes from continuing to administer iodine (orally) for a limited period following the operation, and as some good may occasionally arise, for example in those patients in whom thyroidectomy has been mistakenly carried out before the pre-operative iodine has produced its maximum effect, its use should be continued for one week post-operatively and then stopped. No advantage comes from prolonging its use beyond this period; indeed, if an inadequate operation has been performed it will serve only to mask the return of symptoms. Its prolonged post-operative administration has no preventive action with regard to the development of recurrent thyrotoxicosis.

In post-operative *crisis*, which to-day is only seen in inadequately prepared or antithyroid-resistant cases, iodine should certainly not be deliberately withheld.

Pre-operative Preparation for Third-degree Thyrotoxicosis (Sleeping pulse 110 and above).—Preparation with antithyroid agent and iodine.

Pre-operative Antithyroid Agent.—Patients with severe thyrotoxicosis cannot be brought to a safe operative level without a preliminary course of an antithyroid drug. Administration of the antithyroid agent selected continues in its initial dosage until the patient is symptom-free, or ideally just short of this point, when the drug is stopped altogether. The surgeon's aim is to keep the course as short as possible in order to reduce hæmorrhage at operation and to avoid operating on a hypothyroid patient. A planned pre-operative course of antithyroid agent should rarely exceed four weeks and can often be discontinued with safety after two or three weeks. It is not necessary or desirable to prolong the course until full clinical recovery is achieved, *with the exception of* thyrocardiac patients, the very emaciated, and long-standing cases of neglected thyrotoxicosis. This process will be completed, any remaining toxicity controlled, and the patient brought to a euthyroid state by the pre-operative iodine which follows immediately upon the cessation of the antithyroid treatment.

Pre-operative Iodine.—In calculating the optimum day for operation it is important not to forget to take into consideration the date of onset of the next menstrual period so that this may be avoided.

All patients with thyrotoxicosis being prepared for operation with antithyroid agent must of course receive iodine as well, not so much for its detoxicating action as for its devascularizing effect. In cases of *primary* thyrotoxicosis, if the antithyroid therapy before operation has been prolonged, as in some 'relapse' cases, Lugol's iodine (min. 10 t.d.s. in milk) should be given pre-operatively for a period of at least three, and sometimes four, weeks or it will not produce its full devascularizing effect. The first two weeks of iodine therapy should overlap the last two weeks of antithyroid therapy. The usual short course of 10 days is sufficient in cases of toxic nodular goitre, as they have not the same tendency to bleed.

Those patients who have been receiving the terminal part of their antithyroid course as out-patients may with advantage begin their pre-operative iodine at home. They should return to hospital *not less* than three days before the anticipated day of operation. A post-therapy pre-operative white-cell count should be carried out on the day before operation to exclude a delayed thiouracil leucopenic reaction. A personal visit from the anæsthetist on the day of operation is essential to exclude any contra-indication that may have arisen unexpectedly during the last few days of preparation. If his report is satisfactory and the patient is euthyroid and in good heart, the operation of subtotal thyroidectomy should be carried out.

Post-operative Care—Convalescence.—The ravages of a disease which has been present for months or sometimes years cannot be repaired in a few weeks. A premature return to household or other duties is likely to precipitate an early recurrence of symptoms. The necessary processes of physical readjustment and mental reorientation must be given time to become stabilized. In operation cases it is better that this

interval should be allotted to the post-operative rather than the pre-operative period. Our objective in patients selected for operation should be to restore them to a euthyroid state as quickly as is consistent with safety and then to consolidate this position post-operatively with a reasonable holiday.

LONG-TERM THERAPY—MEDICAL TREATMENT

With Antithyroid Agents

Patients in whom the aim is to achieve stabilization of their thyrotoxicosis by the use of antithyroid agents are treated in the preliminary stages, so far as general management and investigation are concerned, in the same way as patients intended for surgery.

The Resistant—and the Responsive.—There are, however, two uncertainties concerning the action of antithyroid agents which must be solved before their effectiveness for long-term therapy can be known.

First, we have no way of determining beforehand which patients will react favourably (and which unfavourably) to antithyroid agents; *second*, we have no way of predicting which of those patients who do react favourably will be stabilized permanently by their use (or which patients will relapse after treatment and therefore would be better prepared for surgery from the outset). The first step is then to sift the antithyroid-sensitive and -resistant patients from the responsive. This can be done only by resorting to a therapeutic trial with the selected antithyroid agent.

Therapeutic Trial.—To all patients selected for stabilization by medical treatment the procedure recommended is as follows: Give to each a therapeutic test course of antithyroid agent, in order to determine the individual response to the drug.

A *time limit* should be put to this test period of administration. This is because it is now known that those patients who are going to respond favourably, respond *quickly*. Experience shows that there is no advantage in the trial period exceeding two months' duration. In most cases well before the end of this time, three groups will be found to be emerging—the sensitive, the resistant, and the responding. Their future management will now be discussed.

The Antithyroid 'Resistant'.—If no response has been obtained by the end of two months, no response can be expected from the antithyroid agents at present available, however far beyond this period the use of these drugs may be prolonged. If therefore at the end of the two months' trial the patient remains refractory, the antithyroid treatment should be abandoned. It is *at this early stage* that the position of all these patients should be reviewed and a decision taken, and not after months (or even years) of antithyroid therapy. In such non-responding cases the continued use of antithyroid drugs is pointless. From this moment the antithyroid agent should be stopped, iodine started, and thyroidectomy carried out as soon as the maximum response to the iodine has been obtained.

The Antithyroid 'Responsive'.—

Loading Dose.—In responsive patients, and a response is usually noticeable within a fortnight, the selected antithyroid agent is continued in its initial dosage (neomercazole 20 mg. b.d.) until the patient is symptom-free. The view that a temporary *hypo*-thyroid state should be induced at this stage cannot be supported. When symptom-free the dosage is halved (neomercazole 10 mg. b.d.). After being symptom-free for one month the dosage is again halved and is reduced to neomercazole 5 mg. b.d.

Maintenance Dose.—After being symptom-free for three months, a *maintenance dose* of neomercazole 5 mg. daily is instituted and maintained until the patient has been symptom-free for a minimum period of twelve months. The antithyroid agent is then stopped. The patient is provisionally discharged with instructions to report for reassessment in three months' time or before if there is a recurrence of the thyrotoxic symptoms. If this régime is followed, few patients will or should be free from supervision and therapy in less than one year, and some physicians would extend the period of maintenance dosage to eighteen months.

The above is only a rough guide to treatment—some patients are more avid for antithyroid agent than others and a higher maintenance dose may be required—the matter can only be resolved by observing each patient's individual response and adjusting the dose accordingly. If one is to generalize, I would say that the commonest error is to give too high a dosage for too long. Patients should be given a certain responsibility in helping to arrive at the dosage which is best suited to them—in some cases neomercazole 5 mg. or propyl thiouracil 25 mg. on alternate days is a satisfactory controlling maintenance dose. Throughout the initial months of treatment the patient should be seen at *weekly* intervals if myxœdema and the other errors of overdosage are to be avoided. During the period of maintenance dosage the intervals of supervision can be lengthened to once a month. The pattern of equivalent dosages for neomercazole and propyl thiouracil during a 'medical course' of antithyroid treatment is set out in *Table I*.

Table I

	Propyl thiouracil	*Neomercazole*
Loading dose	100 mg. b.d.	20 mg. b.d.
When symptom free (halve)	50 mg. b.d.	10 mg. b.d.
When symptom free one month (halve)	25 mg. b.d.	5 mg. b.d.
When symptom free three months (halve) = *maintenance dose*	25 mg. daily	5 mg. daily

Progress.—Progress is assessed by observing an improvement in the patient's general *clinical* condition—usually first noticed at the end of ten days—by a fall in the basal metabolic rate and pulse-rate, and by an increase in weight. It is, however, a matter for comment that the *tachycardia* in severe cases under treatment with antithyroid agent (*see* Thiouracil Goitre) may persist long after the basal metabolic rate has returned to normal (or is even subnormal) and the other signs and symptoms have improved.

Controls.—A second B.M.R. estimation during the course of antithyroid treatment may be a useful guide to the duration of therapy and occasionally may give valuable warning of *impending hypothyroidism*.

Relapses.—The permanency of the remission induced by the antithyroid substances is not

yet known, as the drugs have only been available since 1943 (Astwood, 1943).

As far as it is possible to judge, approximately half the patients on antithyroid agent alone relapse following the first full course, and a substantial number of those that relapse do so again following a second or third course (Robertson, 1948; Dunlop and Rolland, 1950; Crile and McCullagh, 1951; Douglas and Kennie, 1952; Goodwin and Wilson, 1953). Poate (1950) claimed a cure in 64 per cent of 200 cases treated with methyl thiouracil, but few other workers in this field have had a similar experience. It is doubtful if as many as 40 per cent of those selected for long-term therapy obtain a permanent remission. If this conclusion is accepted it would appear that cases of hyperthyroidism fall into two roughly equal groups: those who have a single non-recurrent bout of the malady, and those who get repeated attacks (Dunlop and others, 1953). Unfortunately as has already been pointed out it is impossible to forecast beforehand to which of these categories a patient belongs or approximately half the patients could be spared a lengthy course of treatment.

Relapses if they are going to occur tend to happen quickly—that is within two to four months of stopping treatment. *Short* courses of antithyroid agent are followed by a *high relapse rate*, so that treatment with antithyroid agents must be continued for a substantial period—not less than twelve months after the patient has become symptom-free.

Treatment of Relapses.—If a patient relapses following antithyroid treatment one should ask oneself two questions: First, was the course maintained for long enough; second, has any feature declared itself during the course which should have inclined one to advise surgery from the start?

In relapse cases a decision has to be taken whether to re-embark upon a further course of antithyroid treatment or whether to switch to surgery. There should be no assumption after the first relapse that all patients should automatically be passed to surgery. Broadly speaking, however, in patients who have relapsed there should be a bias towards surgery, provided experienced surgery is available, but each patient must be individually assessed, bearing in mind on the one hand the tendency for further relapses to occur if the medical treatment is renewed, and on the other the added technical difficulties at operation which are already present following a full course of antithyroid treatment.

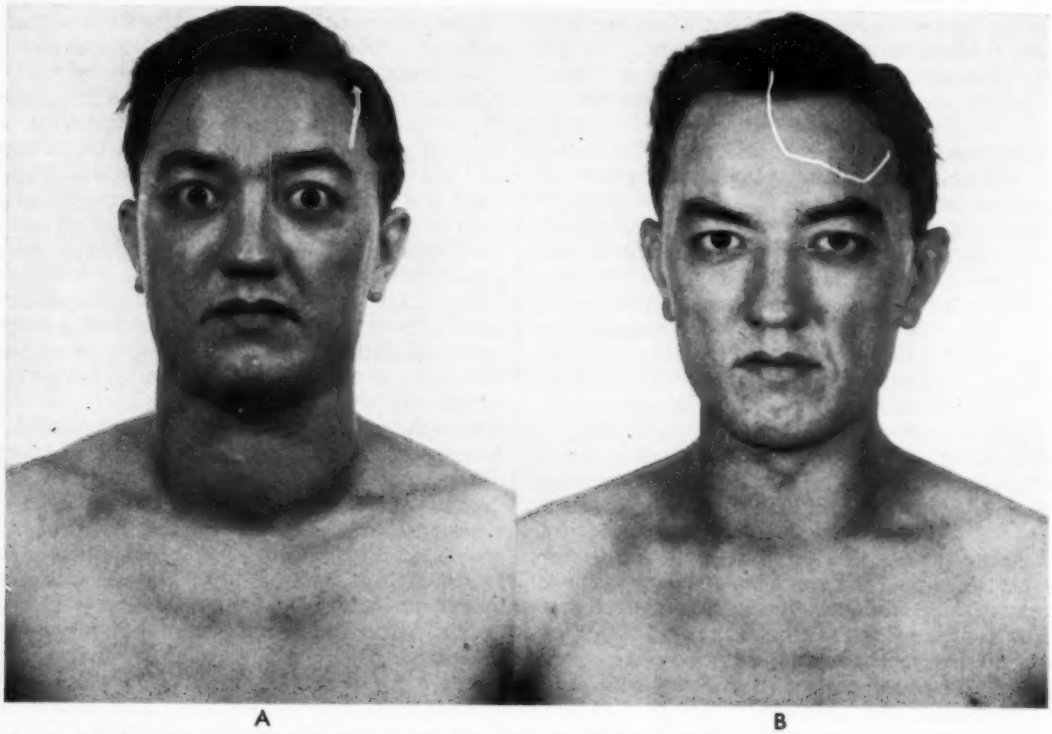


FIG. 41.—*Radio-iodine.* A, Before treatment; B, After treatment (Dr. E. E. Pochin). This patient became intolerant to antithyroid agent and as he could not be brought to a safe operative level was treated with radio-iodine.

Radio-active Iodine

In the Treatment of Thyrotoxicosis.—The effectiveness of radio-active iodine in the treatment of thyrotoxicosis is no longer in question. But with so new and so powerful a weapon it is not surprising that there remain certain problems still to be resolved which for the present restrict its universal application. These problems are essentially twofold.

First: It is not known whether radio-iodine will prove to be carcinogenic in man. It is known to be so in rats (Gredberg and Chaikoff, 1952). It is thought that postradiation neoplasms in man may take twenty years to declare themselves. For this reason, and until we know whether the threats of kidney or bone-marrow damage or the production of genetic mutations are real or groundless, it will be prudent for the time being to restrict the use of

radio-iodine in the treatment of thyrotoxicosis to patients over the age of 45 or those in whom the expectation of life is less than twenty years. It seems likely that the risk of cancer of the thyroid developing subsequently is minimal, so that if the choice lies between death or incapacity from a thyrotoxicosis which cannot be controlled by other means (*Fig.* 41) it will be reasonable as an alternative to advise that the small hazard involved should be taken whatever the patient's age.

Second: The method of calculation of the optimum dosage for a given case of thyrotoxicosis is not yet as accurate as is desirable. Owing to this drawback a certain number of patients (20–50 per cent) receive too little radio-iodine and require subsequent doses (Blomfield, Jones, MacGregor, Miller, and Wayne, 1951; MacGregor, 1954); others receive too much and develop irrevocable myxœdema in up to 17 per cent of cases (McCullagh, 1951; Gordon and Albright, 1950), and in 12 per cent in Blomfield's series (Blomfield, Jones, MacGregor, Miller, Wayne, and Weetch, 1955). It is a matter of experience that the same dose of radio-active iodine will produce a euthyroid state in one patient and myxœdema in another. A relationship between post-operative myxœdema and lymphadenoid changes in the thyroid tissue removed has been demonstrated by Greene (1953), who has shown that the incidence of post-operative hypothyroidism increases directly with the degree of lymphadenoid involvement. It would seem reasonable to suppose that the cases of postradiation myxœdema could be explained in the same way, especially bearing in mind the older age groups that are at present being mainly selected for treatment with the isotope.

Dosage.—The dosage of radiation delivered to the gland is determined by three factors—the proportion of the radio-iodine drink absorbed by the gland, the duration of its stay within the thyroid and the size of the gland itself. These are difficult matters to assess, particularly the size of the gland which still involves a considerable element of guesswork.

An attempt to overcome the disadvantages of the multiple dose method by developing a single dose technique is reported by Fraser, Abbatt, and Stewart (1954). In this method preliminary control of the thyrotoxicosis by an antithyroid agent (neomercazole and *l*-thyroxine) is advocated. By relieving thyrotoxic symptoms rapidly this has an obvious advantage for the patient over the more slowly acting radio-iodine and at the same time by helping to standardize the distribution and retention of the iodine within the gland it is likely to make the calculation of dosage more accurate.

It is not the purpose of this paper to discuss the technical aspects of treatment which have been very fully reviewed by Pochin (1950), Fraser, Ablatt, and Stewart (1954), MacGregor (1954), Blomfield, Jones, MacGregor, Miller, Wayne, and Weetch (1955); nor are we concerned with the place of radio-iodine in the treatment of carcinoma of the thyroid and thyroid metastases or in irradiation ablation of the thyroid; but the types of case in which radio-active iodine may usefully be employed in thyrotoxic patients is of practical importance to the clinician and these will now be mentioned.

Indications.—In my experience radio-active iodine is of particular value in the treatment of patients who are resistant or sensitive to the antithyroid agents, in cases of post-operative recurrent thyrotoxicosis as an alternative to the antithyroid drugs, and in those patients who relapse repeatedly following a full course of antithyroid treatment and who refuse operation. It may be of great value in dealing with advanced thyrocardiac patients. Its use in the treatment of progressive exophthalmos is also being cautiously explored. Radio-iodine is absolutely contra-indicated in *pregnancy* because of the risk of the fœtal thyroid taking up the isotope.

The very simplicity of the treatment naturally makes it popular with patients. The clinical response is slow—one of the disadvantages compared with other methods—and although some improvement may be seen at the end of a fortnight the full measure may not be finally revealed for as long as four months. This could be too long a delay in a seriously ill patient, and in such a case it will usually be advisable to control the thyrotoxicosis in the first instance by the use of antithyroid agent, which is more quick-acting. The clinical response normally follows a similar pattern; in the first few days the gland becomes tender, to be followed in the course of the first week, in some cases only, by an exacerbation of toxicity. In general, primary thyrotoxicosis is a simpler problem for effective and accurate dosage than toxic nodular goitre.

In the Investigation of Thyrotoxicosis.—Owing to the selective affinity of the thyroid gland for iodine the rate of uptake of the radio-active isotope by the thyroid gland itself can be measured by means of a Geiger or scintillation counter. If the amount of radio-active iodine present in the plasma is determined at the same time, the thyroid iodine clearance rate can be measured, and this is of diagnostic value. From the plasma it is removed both by the thyroid and the kidneys. The rate of uptake by the thyroid is related to the activity of the gland, being rapid in toxic goitre and slow in myxœdema. In consequence, during the same period there is proportionately less or more iodine available for excretion by the kidneys, and this amount can be measured.

These variations form the basis of tests which can be used for diagnostic purposes to determine the presence or absence of thyrotoxicosis—and is of value in those doubtful cases in which the clinical picture may be complicated by an anxiety state. It is equally useful in determining the degree of hypothyroidism in a case of myxœdema and can be helpful in circumstances when the B.M.R. is likely to be inaccurate.

During radio-iodine investigations, iodine and the antithyroid drugs should be avoided in premedication before carrying out the tests. Following the normal oral dose of radio-iodine used for tracer work the dosage of radiation received by the ovary with its possible genetic effects is somewhat less than that received by a patient during routine pelvimetry or during the course of a full barium meal. Furthermore, after 24 hours most of the administered dose has either been absorbed by the gland or eliminated by the kidneys.

To summarize, it is probably reasonable to say at the present time that radio-active iodine when

used for purposes of investigation as opposed to therapy has its greatest application as a research tool and is of less value and is less necessary as a diagnostic aid.

The Operation

Subtotal Thyroidectomy for Toxic Goitre.—There is one essential prerequisite to surgery—namely, that the toxic goitre shall have been converted into a non-toxic goitre by the day of operation. It is, however, particularly important to make sure that this objective has not been exceeded and a hypothyroid state induced. If the patient has been

FIG. 42.—Adherent puckered scar due to central drainage.

rendered myxœdematous it is dangerous to operate until this has been corrected. Myxœdema may produce œdema of the glottis and thickening of the vocal cords, which is accentuated by the manipulation of the operation. When the indwelling intracheal tube is removed post-operatively the airway may be seriously threatened and a dangerous and alarming stridor develop for which in serious cases the only satisfactory measure is a tracheostomy.

The purpose of the operation is quantitatively to reduce the number of functioning thyroid units and so to restore the patient to thyroid balance. Provided the four named arteries to the gland are tied, I do not believe that it is either necessary or desirable to perform the extremely radical thyroidectomy, removing seven-eighths or even nine-tenths of the gland, that has been advised and practised in the past. This was done because, in the absence of antithyroid agents, the threat of recurrent post-operative thyrotoxicosis was a more difficult problem than the treatment of a possible myxœdema, for which thyroid was available. The reverse holds to-day.

In my opinion it is preferable to leave approximately one-sixth of the gland, removing the isthmus, the pyramidal lobe, and five-sixths of the lateral lobes, which is still a substantial proportion, and to risk the possibility of recurrent thyrotoxicosis, for which we now have remedies that were not available a few years ago. This is still a subtotal thyroidectomy and has the added, though subsidiary, advantage that there is less likelihood of removing one or more of the parathyroid glands and of picking up the recurrent nerve when suturing the cut surface of the gland. It is a matter of opinion, but in my experience recurrent thyrotoxicosis—and it is rare—is much more amenable to effective and lasting treatment than myxœdema, in which the patient's whole constitutional make-up may become involved.

Hemithyroidectomy (partial thyroidectomy ; unilateral lobectomy) has no place in the treatment of diffuse toxic goitre.

It is not the purpose of this article to discuss technical details but attention is drawn to the following points :—

Toxic Adenoma.—In my experience it is not necessary to perform a bilateral operation for a unilateral ' toxic adenoma ' provided the contralateral lobe is explored at operation and appears normal to palpation and inspection.

The Superior and Inferior Thyroid Arteries.—When the subtotal operation is performed for thyrotoxicosis the superior thyroid arteries should be tied and divided and the inferior thyroid artery tied in continuity on each side. There is an abundant blood-supply left to the gland by way of the paratracheal and para-œsophageal branches of the ascending pharyngeal and bronchial arteries. Ligation of the inferior arteries—as far away from the gland as possible—to avoid injury to the recurrent nerve, has two great advantages : it reduces the incidence of recurrent thyrotoxicosis ; and it reduces the bleeding from the cut surface of the gland when this is resected.

In patients who before preparation for operation were very severely toxic, the inferior arteries, as is the usual practice with the superior arteries, should be tied and *divided.* One must beware of tying one of the main terminal divisions in mistake for the main trunk, which may bifurcate far out.

In thiouracil-prepared cases it is dangerous to attempt the resection of the gland until all the named arteries have been secured or an uncontrollable fatal hæmorrhage may result from the cut surface. The ' clip and cut ' method has no place in the operation on these patients.

Multiple-stage Operations.—It is difficult to visualize the circumstances in which the preliminary ligation of arteries could arise to-day unless the toxicity is quite uncontrollable by the medical methods which are now available. On the other hand it may occasionally be both prudent and necessary to stop the operation after resecting one lobe and to operate on the second side at a later date. The need for such a two-stage thyroidectomy is most likely to arise when operating on a very vascular hyperplastic gland in a young person who has received too long a pre-operative course of antithyroid agent or who has relapsed after long-term therapy. The operation under these conditions can be one of the most testing in surgery and if the hæmorrhage is unusually heavy or if the pulse-rate should rise to 140 or above it would be foolish to proceed to the resection of the second lobe. Indeed, it is a surgeon's duty to content himself, after the ligation of the superior and inferior thyroid arteries (which are always considerably enlarged after antithyroid treatment and therefore the more easily negotiated) with the resection of one lobe.

The Infrahyoid (Strap) Muscles.—Very few special manœuvres in surgery should be executed routinely

—although the general pattern of an operation should be standardized. A good working rule is that the muscles should be divided in all cases in which the added exposure would be an advantage in mobilizing the lobe concerned. Division of the muscles is indicated more often in bilateral than unilateral operations. It should be carried out in all operations upon glands which have been prepared with an antithyroid agent unless the surgeon is exceptionally experienced; it is usually unnecessary in partial thyroidectomy (hemithyroidectomy) for a solitary adenoma.

Drainage.—There is nothing to be lost by drainage, and, unless the operation area is exceptionally dry, it pays to drain. Drainage should be of the simplest kind—with the corrugated drain emerging *laterally*, at the extremities of the wound, and never from its centre or puckering will follow when the patient swallows (*Fig.* 42). If the muscles have not been divided a single piece of dam should be laid subcutaneously—immediately beneath the skin-flaps. When a subcutaneous drain has been used, the pretracheal fascia should never be completely sewn up in the midline or a tension hæmatoma may develop deep to it and cause sudden and severe dyspnœa. If an opening is deliberately left in the deep fascia and bleeding from the gland does occur the blood is able to escape subcutaneously (*Figs.* 43, 44).

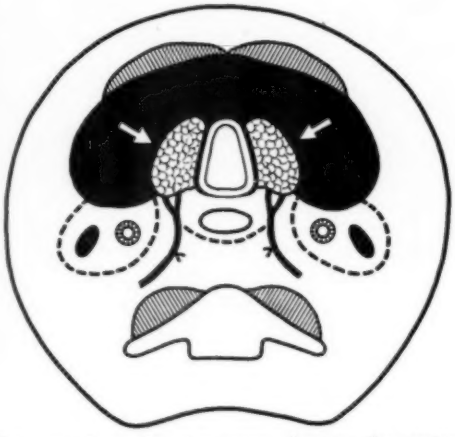


FIG. 43.—A tension hæmatoma deep to the pretracheal fascia, which has been sewn up. Removal of skin stitches and Michel clips will not adequately release the pressure on the trachea.

FIG. 44.—Escape of blood is possible through the opening in the pretracheal fascia into the subcutaneous tissues.

If the muscles have been divided two pieces of dam will be required, the central ends directed into the deep compartment alongside the remnants of the gland, their outer ends emerging laterally (at the extremities of the wound), between the strap muscles and anterior border of the sternomastoid. Drainage by a stab wound through the strap muscles is unsatisfactory as it may set up bleeding on its own from the opening in the muscles. The drainage dam is ordinarily removed on the morning following the operation, but after operation on antithyroid-prepared glands it should be left in for a full 24 hours.

Post-operative Complications

The operative mortality and the incidence of post operative recurrent thyrotoxicosis, myxœdema, and tetany will now be discussed. The clinical material in this series consisted of 250 patients (126 with second-degree thyrotoxicosis; 124 with third-degree thyrotoxicosis) who were operated upon for toxic goitre (non-toxic goitre is excluded), either by unilateral operation (33) or by subtotal thyroidectomy (217).

Operative Mortality.—There has been an appreciable reduction in the operative mortality of thyroidectomy for toxic goitre since the introduction of the antithyroid agents. Examples of thyroidectomy mortality-rates in the prethiouracil era are given by Wallace and Wevill (1933) 12·3 per cent; Silverstone (1934) 8 per cent; Graham (1939) 2·9 per cent; Poate and Wyndham (1940) 3·1 per cent; Short (1941) 7·6 per cent.

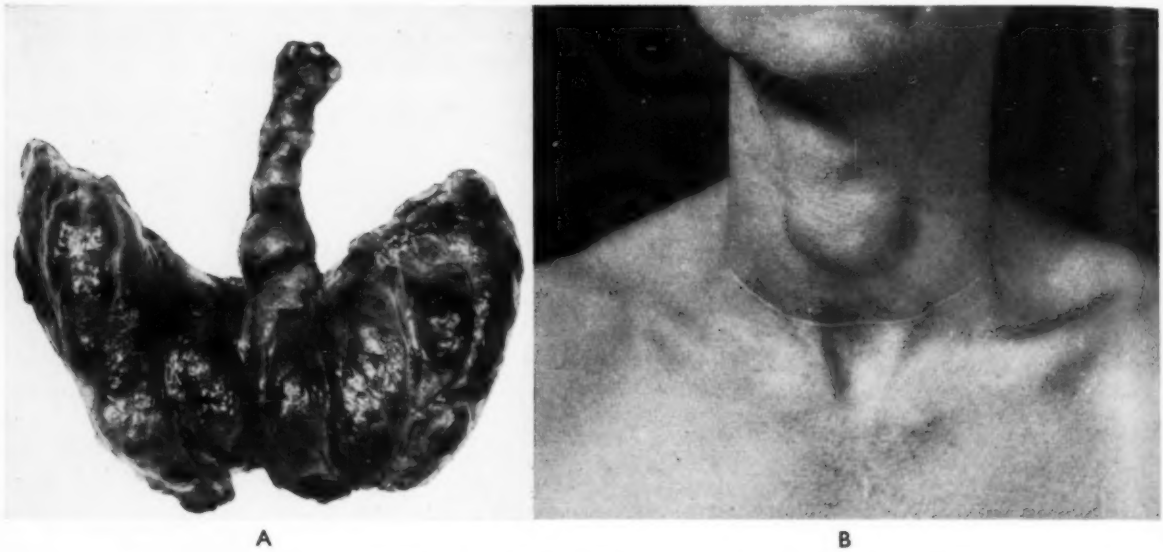
In this series of 250 patients operated upon for toxic goitre (since the introduction of the antithyroid agents) 2 died as a result of the operation, making a case mortality-rate of 0·8 per cent. Operative mortality-rates reported by authors since 1943 include: Williams (1949) 1 per cent; Piercy (1947) 0·6 per cent; MacKnight (1947) 0·3 per cent; Cole (1944) 1·14 per cent; and Armitage (1956) 0·8 per cent, who had 7 deaths in 886 thyroidectomies for toxic goitre.

These figures relate to operations which were carried out in specialized clinics. In non-specialized clinics the mortality-rate is probably considerably higher.

Post-operative Thyroid Crisis.—Post-operative thyroid crisis should be rare but can still occur. It was seen in one of my two post-operative deaths recorded above—a thyrocardiac patient with a toxic nodular goitre resistant to the antithyroid agents (and operated upon before the introduction of radio-iodine). The prevention of thyroid crisis depends upon the conversion of the toxic goitre into a non-toxic goitre before operation.

Post-operative Tetany.—Post-operative tetany may be mild and transient or acute and permanent. In the series under review there were 217 subtotal thyroidectomies for toxic goitre and 3 instances of the mild and transient form of tetany (1·4 per cent).

The predominant symptom in each was carpopedal spasm, and this appeared within 48 hours of the operation, and responded in all cases to a single intravenous injection of 10 c.c. of 10 per cent calcium gluconate. In the acute cases the beneficial and dramatic effects of the intravenous calcium are, however, but temporary, and measures must be taken to ensure a more sustained elevation of the blood calcium. In the first instance this is best obtained by the intramuscular injection of parathormone, but in the course of a few days the injections become progressively less effective and require to be replaced by dihydrotachysterol (A.T.10, or antitetanic preparation No. 10) which has the advantage that it can be administered by mouth. The danger associated with this drug is that of producing hypercalcæmia, so that as small doses as are compatible with maintaining a normal serum-calcium should be used. In addition, as a protection, it is wise to supply calcium salts by mouth, which may be taken in the form of calcium lactate, thrice daily, together with a diet high in calcium content—milk, cheese, etc. (Mason and Zintel, 1946).



A B

FIG. 45.—A, *Pyramidal lobe* (operation specimen); B, *Pyramidal lobe* (recurrence).

Post-operative Recurrent Thyrotoxicosis.—A return of true toxic symptoms after a carefully planned and executed subtotal thyroidectomy should be rare. There are two main causes: (1) Failure to remove sufficient glandular tissue; (2) Failure to ligate the inferior thyroid arteries.

Inadequate Resection.—Hæmorrhage is the factor which most commonly predisposes to inadequate resections. If the operation is hurriedly performed or the resection attempted in a field obscured by hæmorrhage it is likely that too little gland will be removed and an early recurrence may be expected. Failure to remove the pyramidal lobe may occasionally be responsible for a recurrent attack (*Fig.* 45).

Failure to Ligate Inferior Thyroid Arteries.—It has always been my practice to tie the inferior thyroid arteries in continuity on both sides, unless I could not find them, when operating on a toxic goitre. Piercy (1947), reporting 550 thyroidectomies for toxic goitre in which the inferior thyroid arteries were tied, claimed no known recurrences, compared with a 6 per cent recurrence rate in a series of 750 thyroidectomies at the same hospital in which the arteries were not tied. In my series 250 patients have been seen regularly by myself since their operations and 5 have developed a toxic recurrence (2·0 per cent). There was diffuse regeneration in 4 patients and nodular regeneration in 1 patient. There was also pyramidal lobe regeneration in 2 other patients, but without return of toxic symptoms. During the same period there were 9 other cases of recurrent post-operative thyrotoxicosis in patients who had had their primary operation elsewhere. All these patients were individually interviewed and no doubtful case has been excluded. All have responded to treatment either with antithyroid agent or radio-iodine or with re-operation, and all are now in normal health.

Post-operative Myxœdema.—If the *somewhat* less radical thyroidectomy recommended for toxic goitre becomes more generally practised, tetany and myxœdema should virtually disappear as post-operative complications. Post-operative myxœdema, while not so serious as the persistent form of tetany, is certainly undesirable as permanent substitution therapy with thyroid extract may be necessary. In contrast, post-operative recurrent thyrotoxicosis usually responds rapidly to treatment and rarely if ever requires permanent medication. In my series of 217 bilateral operations there were 8 instances of myxœdema (3·6 per cent), of which 3 are likely to require thyroid substitution therapy for the rest of their lives. The treatment of adult myxœdema has been called "as perfect a form of therapy as any known to medicine" (Means, 1937). This may be so, and is indeed fortunate if the myxœdema is established or inevitable, but the replacement of one disease by another cannot by any standards be regarded as the ideal termination of a therapeutic process. Our aim to-day should be to avoid altogether promoting operation-induced myxœdema in

toxic goitre. (In non-toxic goitre the position is entirely different as the degenerating gland may be almost functionless and the patient verging on myxœdema before the operation is undertaken.)

SUMMARY

Great strides have been made in the last ten years in methods of controlling thyrotoxicosis. Surgery, the antithyroid drugs, and radio-iodine are now available, and each has its advantages and disadvantages.

1. The object of this paper has been to balance the conflicting claims of short-term and long-term therapy, and in so doing to indicate how the clinician may set about determining which of these particular methods is best suited to a particular patient.

From the point of view of treatment patients with thyrotoxicosis fall into two broad categories : on the one hand there are those who present with some special feature which is sufficiently well marked to be a decisive indication from the first either for medical or for surgical treatment ; and on the other there are those in whom there is no clear-cut indication present as to which method of treatment would be most appropriate. In this indeterminate group the decision as between long-term or short-term therapy can only be resolved after a period of observation and after reviewing such factors as the patient's age, the facilities available, and the presence or absence of a precipitating factor. Once these data have been assessed it is urged that the next step in the sequence of events should be to consider the desirability or not of surgery. It is irresponsible as a first measure to try antithyroid methods on all patients indiscriminately and to pass to surgery only those labelled 'failed medical treatment'. From the patient's point of view the success of treatment depends upon the skill with which this *early selection* process is effected.

2. The opinion is expressed that age offers the best guide in deciding upon the definitive line of treatment in this indeterminate group and that within a wide latitude surgery is indicated in younger adults (aged 18 to 40) and medical methods in the more elderly. This conclusion has only been arrived at after reflecting upon the high relapse rate associated with the antithyroid drugs, the hyperplastic response of the thyroid gland itself to these drugs, and the tedium associated with prolonged treatment and supervision. Naturally the decision to advise surgery at any time is dependent upon experienced surgical help being available.

3. *Medical treatment* is indicated at the extremes of life, that is in children and in the elderly ; at times of unusual but passing stress, such as puberty, pregnancy, and the menopause ; and in patients with mild thyrotoxicosis, recurrent post-operative thyrotoxicosis, and masked thyrotoxicosis.

The application of the *antithyroid drugs* for long-term and short-term therapy differs. The essential feature of *long-term* therapy is that the patient is taken to full clinical recovery and is thereafter kept in the euthyroid state on a maintenance dose of antithyroid agent for at least one year. The essential feature of *short-term* therapy is that the pre-operative course of antithyroid agent should be as brief as is consistent with bringing the patient to a euthyroid state by the day of operation.

While this expeditious method can be applied to the majority of patients requiring pre-operative preparation with antithyroid drugs there are some—notably certain thyrocardiac patients, those who have lost weight excessively and long-standing cases of neglected thyrotoxicosis—who should be taken to full clinical recovery and held there by antithyroid agent in reduced dosage until their body-weight has returned to normal and they have had an opportunity to build up a constitutional reserve.

4. It is particularly emphasized that in those patients selected for surgery at the outset, special care should be taken to determine whether antithyroid agent is in fact needed (in addition to iodine) to bring them to a safe operative level ; and that in those patients selected for long-term therapy at the outset, their response to antithyroid agent should be reviewed not later than two months after commencing treatment, so that those who are not responding satisfactorily may be recognized early and their treatment by these drugs discontinued.

5. Attention is drawn to the errors of overdosage, to the toxic granulopenic reaction, and to the danger of operating on the hypothyroid patient.

6. *Radio-iodine* has great potentialities and in theory this treatment is ideal but it is not yet universally available. It is absolutely contra-indicated in children and pregnant women. It has its most valuable application in the treatment of patients who are resistant or sensitive to the antithyroid drugs and in the treatment of post-operative recurrent thyrotoxicosis as an alternative to the antithyroid drugs. Its future, if the incidence of induced myxœdema can be reduced and the threat of carcinogenesis be shown to be theoretical, is almost certain to be an expanding one.

7. The *surgery of the thyroid gland* has also kept pace with the other advances in antithyroid treatment, and is now safer and surer than it was a decade ago. In skilled hands and in combination with careful medical preparation and selection it still holds pride of place as the most generally applicable method of treatment. The subtotal operation is preferred to the near total thyroidectomy, because—of the glandular complications of the operation—post-operative recurrent thyrotoxicosis is now more readily controlled than post-operative thyroid insufficiency, which requires permanent substitution therapy.

8. Finally for the truly successful management of thyrotoxicosis, whatever the treatment, the patient's confidence is essential. To get this and to keep it, continuity of supervision is vital, and this must be personal and constant—not impersonal and changing.

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PER-OPERATIVE MANOMETRY AND RADIOLOGY IN BILIARY TRACT DISORDERS

BY PIERRE MALLET-GUY, LYONS, AND J. DUDFIELD ROSE, NEWCASTLE UPON TYNE

THE purpose of this paper is to describe a technique of manometric and radiological control of biliary tract surgery to be carried out at the time of operation. The technique gives precise information on biliary tract function and more exact information on morphological change than is possible from visual and tactile examination or from instrumental probing of the tract, which can be dangerous. The technique is comparatively simple and does not prolong the operation for more than ten to fifteen minutes. During the last ten years the technique has undergone simplification and as far as possible all causes of error have been removed so that it is now possible to assess biliary tract function accurately and to demonstrate clearly morphological change.

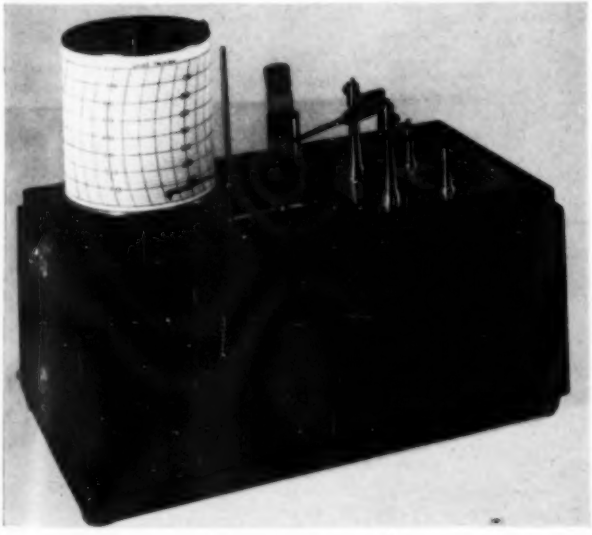

FIG. 46.—The recording manometer.

In 1586 Marcellus Donatus in his *De Historia Mirabilis* records that Silviaticus first observed gall-stones in 1317. Van der Weil appears to have been the first to remove gall-stones in 1667, but it is most likely that he only incised an abscess containing stones. It was not until 1878 that Kocher recorded the first successful cholecystostomy, and on July 15, 1882, Langenbuch performed the first cholecystectomy on a 43-year-old man in the Lazarus Krankenhaus in Berlin. For the next few years both operations had their protagonists. In 1914 W. G. Crile advocated cholecystostomy as the better operation,

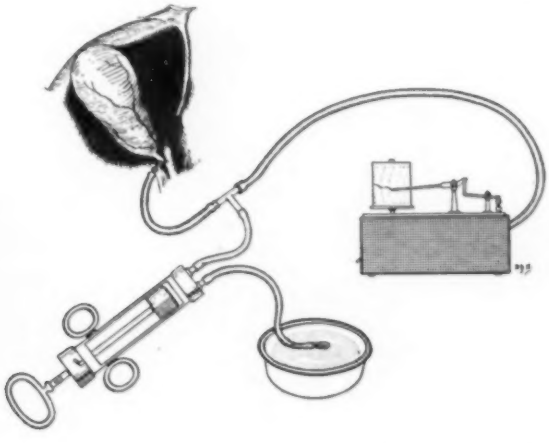

FIG. 47.—Diagram showing the arrangement of the pressure recording apparatus.

and two years later Rutherford Morison (1916) was advocating conservatism. He also described an operation which he called cholecystendesis; this consisted of carbolizing the interior of the gall-bladder in order to destroy the mucosa and reduce the organ to a fibrous mass. This he did when the gall-bladder was adherent and removal would be dangerous. Soon critical surveys of series of cases began to appear; in 1919 W. H. Magie questioned the advisability of removing a comparatively healthy gall-bladder just because it contained stones. F. D. Moore (1921), in a comparative study of 3000 cases from the literature and 250 of his own, stated that cholecystectomy was the operation of choice. In the following year James Sherren reviewed the situation in an article in the BRITISH JOURNAL OF SURGERY

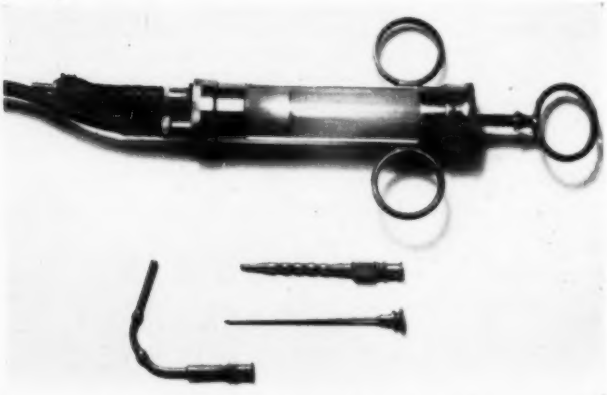

FIG. 48.—The two-way syringe and cannulæ.

FIG. 50.—Sketch of the method of centring the X-ray plate.

FIG. 49.—The apparatus in use.

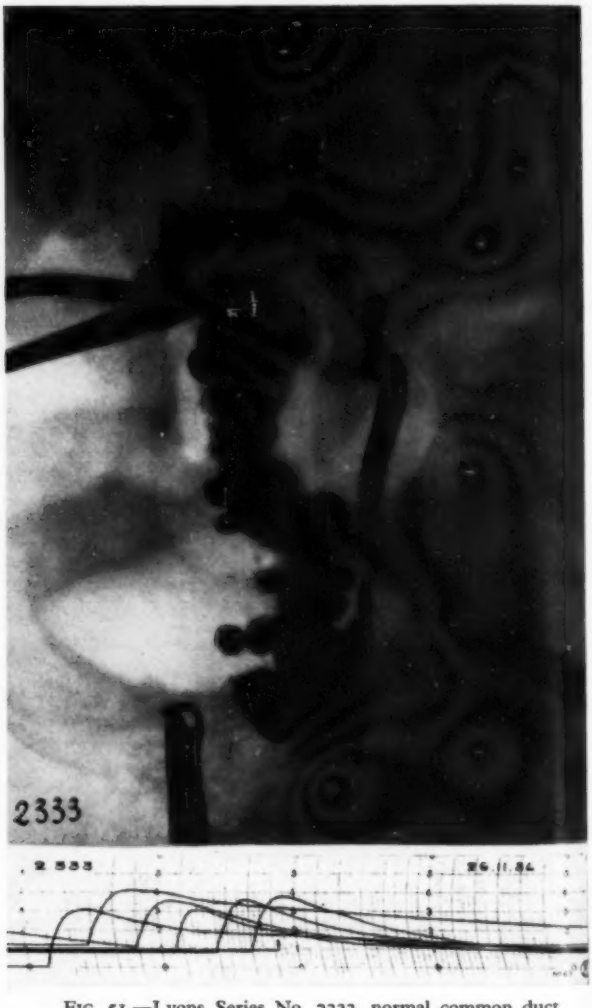

FIG. 51.—Lyons Series No. 2333, normal common duct. A normal intraduct pressure and normal cholangiogram.

and stated that in a series of 100 cases of gall-stones he had removed the gall-bladder 94 times, but in a similar series ten years previously he had removed the gall-bladder in only 29 cases. Attention was still largely concentrated on the problem of whether cholecystectomy or cholecystostomy should be performed and in perfecting the technique of these operations. It soon became clear that cholecystectomy was the better operation, and by 1929, when Cattell reviewed 250 cases, surgeons were recording the long-term results of these operations. Cattell advised that cholecystectomy was the better operation, but showed quite clearly that neither operation was without post-operative morbidity. Moore as early as 1921 only claimed that 70 per cent of his cases were completely cured, 20 per cent were improved, and 10 per cent were bad results. In 1938 Hellstrøm, of Stockholm, reviewed 1041 cases and found that nearly 30 per cent had biliary pain after cholecystectomy and only 30 per cent were symptom-free. R. L. Saunders (1943), however, maintained that out of 3000 cases 90 per cent were cured, and he attributed this high rate of cure to the rigid selection of cases for operation. In more recent years Hu. C. Myers (1953) followed up 280 cases of cholecystectomy, of which 20 per cent had persistent pain after operation, and he also pointed out that in non-calculous cholecystitis, pain occurred in an even higher percentage (60 per cent). Walter Hess (1955), of Basle, stated that only 43 per cent of patients were free from pain after cholecystectomy. One cannot escape the conclusion that the criteria of cure were not as rigid as the indication for operation in many series. It is our impression that only about 65 per

FIG. 52.—Lyons Series No. 2470, choledochlithiasis. The graph shows typical blockage curves, each stabilized pressure being higher than the one preceding. The cholangiogram shows a widely dilated and blocked duct. Some of the contrast material has passed round the stone and outlined it.

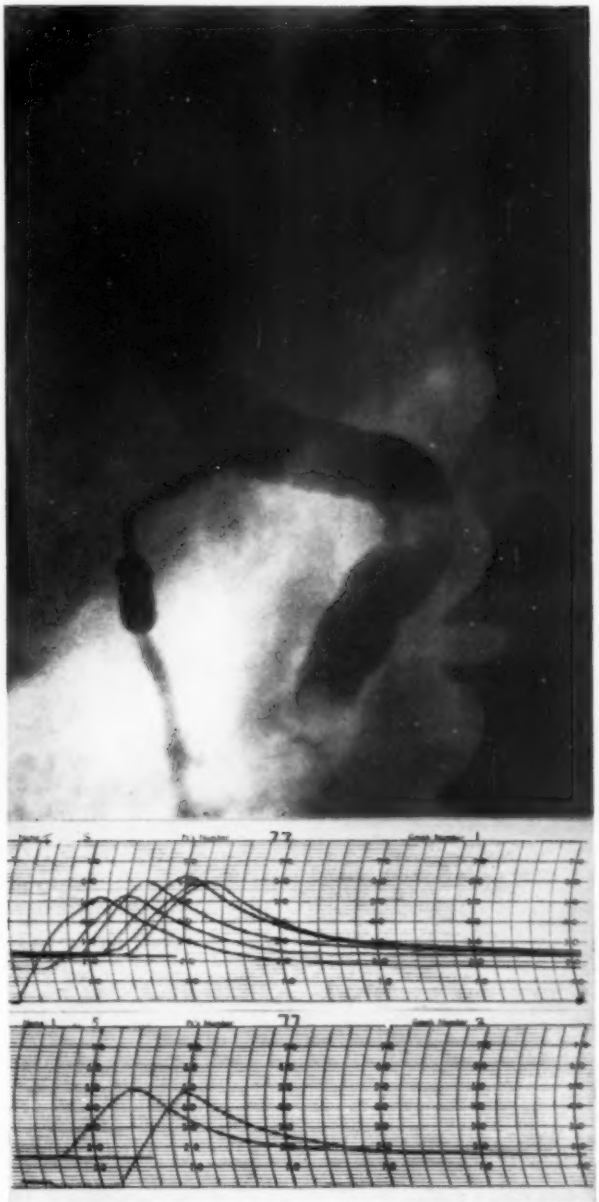

FIG. 53.—Newcastle Series No. 77, choledochlithiasis. Graph No. 1 shows that the pressure within the common duct stabilized at 22 cm. of water. The cholangiogram shows a dilated and tortuous common duct which contains several stones, one of which is impacted in the ampulla of Vater. Graph No. 2, taken after the removal of the stones, shows that the pressure had stabilized at 13 cm. of water.

cent of patients are free from symptoms and dietary restrictions. In a series of 100 cases recently followed up by one of us (J. D. R.), 34 are unsatisfactory, and of these at least half felt as severe discomfort after as before operation and some felt definitely worse. It cannot be denied that cholecystectomy leaves much

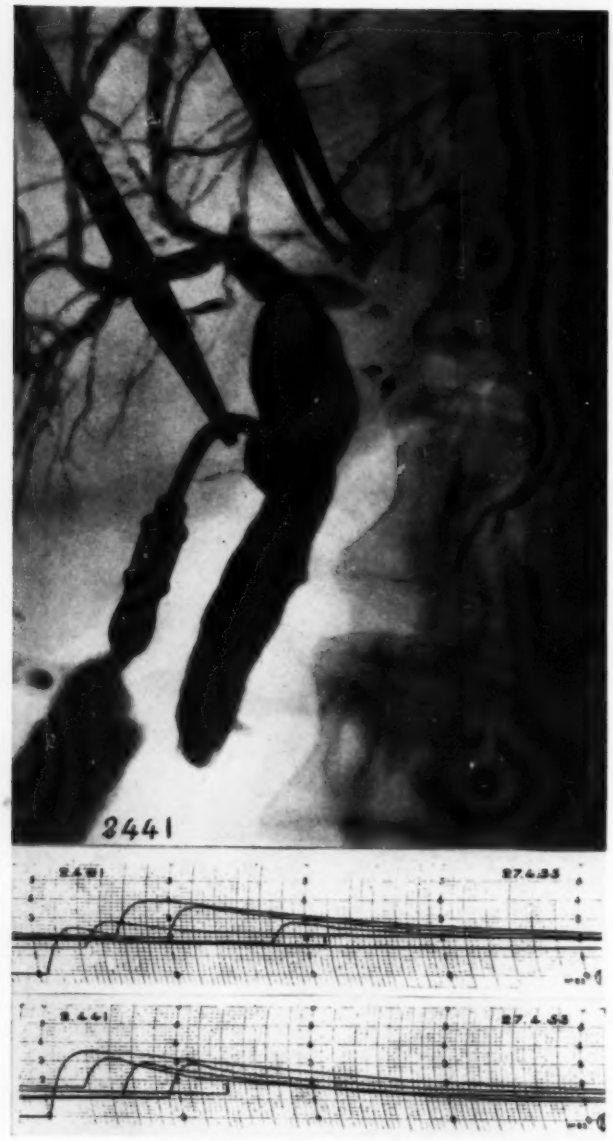

FIG. 54.—Lyons Series No. 2441, post-cholecystectomy syndrome, fibrosis of the sphincter of Oddi. The first graph shows the pressure taken in the common duct stabilized at 15 cm. of water. The cholangiogram shows a dilated common duct with a marked hepatic reflux. The duct terminates in a pencil point. The second graph taken after sphincterotomy shows that the pressure had fallen to 12 cm.

to be desired and biliary surgery leaves many problems unsolved, the most important of which is the persistence or recurrence of symptoms after operation. The realization of this has led investigators to search for better and newer methods. Surgeons are turning their attention from purely morphological changes to functional changes, realizing that a disordered function very often precedes or accompanies a disordered morphology.

Many surgeons have explored cases of post-cholecystectomy failure and only in the minority of cases have they been able to find any morphological change to which the cause of failure could be attributed. It became clear that technical error could not be the cause of any but a small number of

FIG. 55.—Newcastle Series No. 93, spasm of the sphincter of Lütcken. Graph No. 1 shows a typical set of blockage curves. The cholangiogram shows a distended tense gall-bladder and a normal common duct which is emptying into the duodenum normally. The second graph, taken after the injection of Xylocaine into the vagus, shows that the pressure had stabilized at 19 cm. of water.

failures. Greater attention began to be paid to the function of the biliary tract, which, like the intestine, has the general functions of absorption, secretion and motor activity, of which the motor activity is

the most important. The main function of the biliary tract is after all the propulsion of bile from the liver to the intestine.

One of the earliest workers to study the motor function of the biliary tract was Doyon (1893) who in Lyons not only studied the contractility of the biliary tract but devised means of recording its movements. Even before Doyon, Heidenhain in Breslau had measured the pressure in the biliary tract as early as 1868. Oddi in 1888 attributed the pressure in the biliary tract to the tone of the common duct sphincter which now bears his name. Since those early workers there have been many others who, like Herring and Simpson (1907), studied the pressure of bile secretion, Judd and Mann (1917), Potter and Mann (1926) who studied pressure changes in the biliary tract, MacGowan, Butch, and Walters (1936) studied the biliary tract pressure and its relation to pain, and Doubilet and Colp (1937) studied the resistance of the sphincter of Oddi.

It was by accident in 1918 that Reich first demonstrated the possibility of rendering the biliary tract opaque to X rays; then followed the works of Tenny and Patterson (1922), Carnot and Blamoutier (1922), Lunari and Squirru (1924), and Cotte (1925). But it was Mirrizi (1932) in Cordoba in 1931 who took the most important step forward by showing the possibility of demonstrating the bile-ducts during operation.

Here we have two of the most important methods of studying both biliary function and morphology by the measurement of biliary pressure and the radiological demonstration of the biliary tract. It was in 1942 that one of us suggested the per-operative manometric and radiological examination of the biliary tract, and showed their value in the diagnosis of functional disorders and of morphological change. Since that time more than 2500 cases have been operated on using these methods, which have been applied to all cases coming to operation. The technique is simple and safe and adds only 10–15 minutes to the operating time.

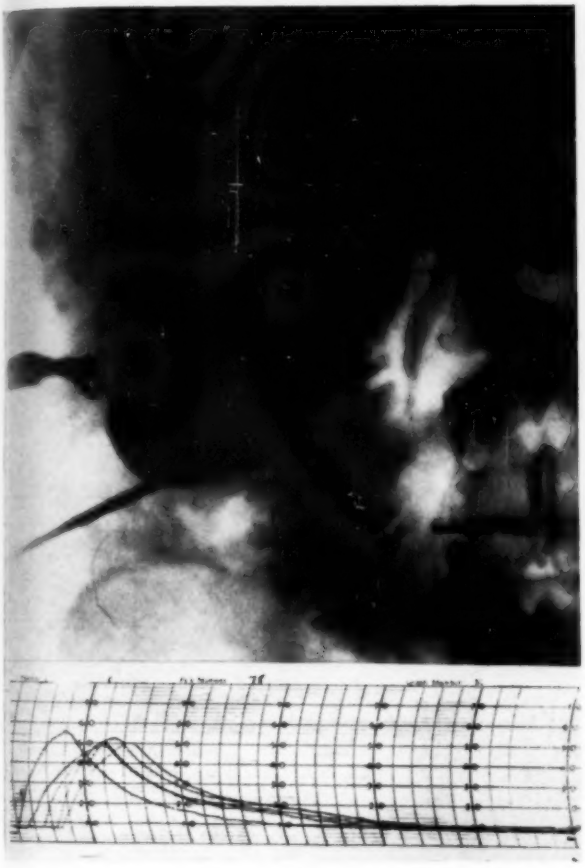

FIG. 56.—Newcastle Series No. 78, generalized hypotonia. The graph shows that the pressures taken in the gall-bladder stabilized at 8 cm. of water. The cholangiogram shows a large gall-bladder and a normal common duct with a widely patent sphincter of Oddi, and much of the contrast material in the duodenum.

FIG. 57.—Lyons Series No. 2442, hypotonia of the common duct. The graph shows a gross degree of hypotonia, the common duct pressure stabilized at 0 cm. of water. The cholangiogram shows a dilated common duct with a widely open sphincter of Oddi, and a reflux along a widely dilated duct of Wirsung.

TECHNIQUE

The investigation is divided into two parts which follow one another immediately. The first is the measurement of the pressure within the biliary tract, the second is the taking of a cholangiogram. The

type of anæsthesia is of prime importance and allows of no deviation whatever (Feit, Rademaker, and Trias Farcas, 1951). It has been found experimentally that a nitrous oxide, oxygen, and ether anæsthetic within the limits of surgical anæsthesia has no effect on the biliary tract function, nor is alteration caused by performing a laparotomy (Feit, 1951). Experimental evidence shows that the biliary pressure is under sympathetic and vagal control and any drugs which alter the equilibrium between these two systems must be rigidly avoided. This precludes the use of the usual drugs given as premedication. Also any gross alteration in blood-pressure will alter the biliary pressure, so that vaso-constricting drugs should also be avoided until after the investigation is completed. Should a state of shock supervene and it is necessary to give such drugs to resuscitate the patient, then the pressure readings should be disregarded.

The pressure within the biliary tract is recorded on a manometer which resembles the usual self-recording barograph, the drum revolving once in thirty seconds (*Fig.* 46). The pressure capsule is connected by means of tubing to the biliary tract, in the following manner: a tube connected at one end of the manometer and at the other end to a T junction, passes over a support 2–3 ft. above the level of the patient. To one of the other limbs of the T piece is attached a syringe for the injection of the fluid; from the third limb a tube leads to the cannula, which is inserted into the biliary tract (*Fig.* 47). It is convenient to use a syringe which is fitted with an inlet and outlet valve (*Fig.* 48). To record the pressure about 5 c.c. of normal saline at body temperature are injected into the system. Part of this flows up the tube going to the manometer and part flows in the opposite direction into the biliary tract (*Fig.* 49). While this is being done the needle of the manometer rapidly rises to a pressure of about 40–50 cm. of water (it must be remembered that this is not the pressure within the biliary tract at the moment; it is the pressures in the tubes proximal to the cannula, the actual pressure in the duct is much lower). When the injection is ended the pressure recorded on the manometer begins to fall and the fluid in the tubing flows into the biliary tract under a falling pressure until an equilibrium is reached between the pressure and the tone of the sphincter mechanism. Provided the pressure rise produced in the biliary tract is greater than the sphincter will hold, then the fluid will flow into the intestine until a pressure is reached which the sphincter will hold, at which level the needle will cease to fall and record a steady line, which is the stabilized pressure. The manœuvre is repeated several times until the stabilized pressures are

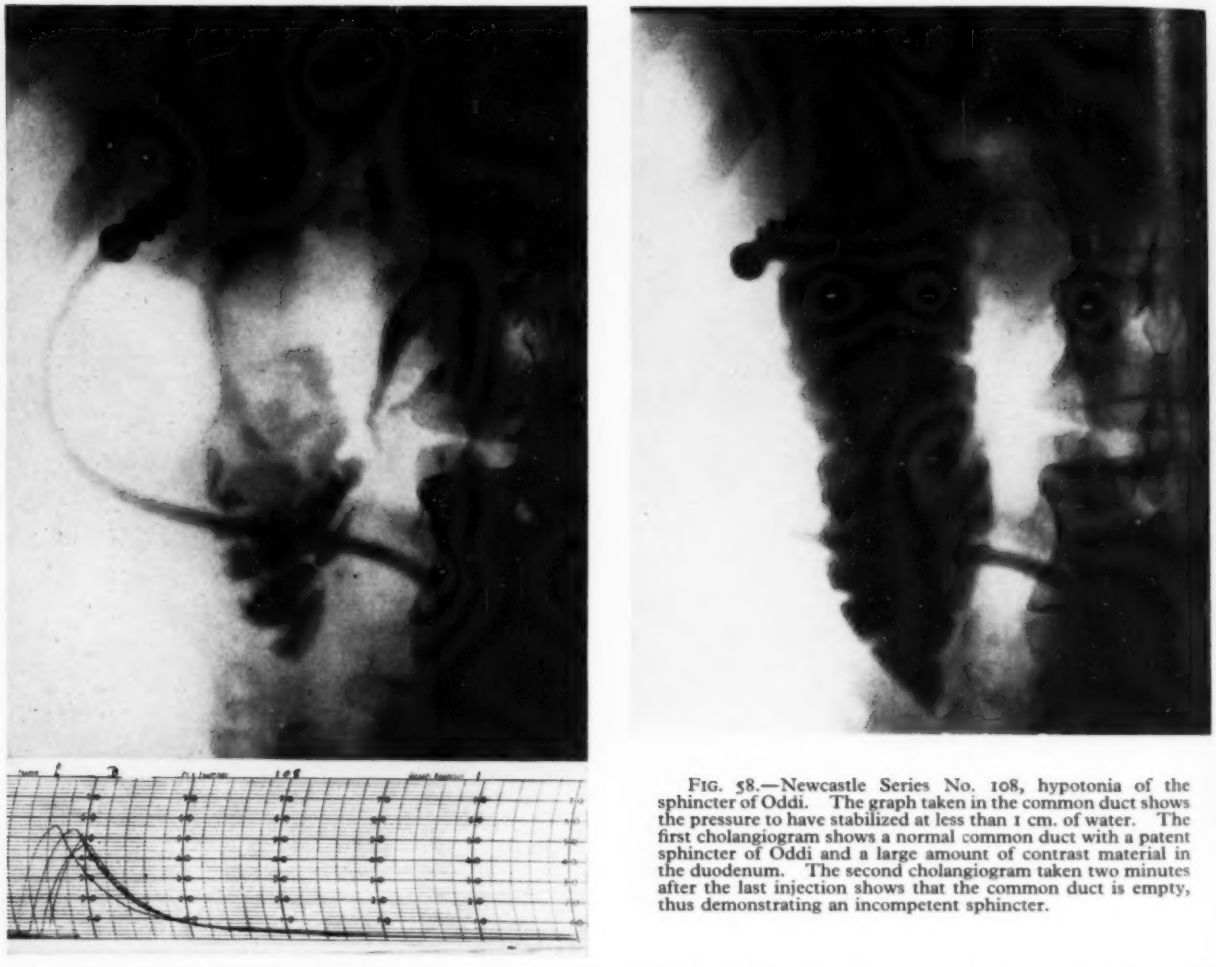

FIG. 58.—Newcastle Series No. 108, hypotonia of the sphincter of Oddi. The graph taken in the common duct shows the pressure to have stabilized at less than 1 cm. of water. The first cholangiogram shows a normal common duct with a patent sphincter of Oddi and a large amount of contrast material in the duodenum. The second cholangiogram taken two minutes after the last injection shows that the common duct is empty, thus demonstrating an incompetent sphincter.

uniform or nearly so. It is important that the cannula diameter should not be less than 2·5 mm. in order to avoid capillary resistance.

The second investigation, the taking of a cholangiogram, follows immediately on the manometry. It is important that the X-ray plate should be centred correctly, and one of us (M.-G., 1947) has devised a simple means of ensuring this (*Fig.* 50). Using an operating table of wood or aluminium, the X-ray tube is placed below the patient and the plate above. Both the tube and the plate holder are mounted on one bracket so that they move together. On the plate holder the central point is marked by two cross-lines. A small spotlight is held on a stand immediately above the patient and illuminates the common duct by means of a pencil beam of light. When the exposure is to be made the plate holder and X-ray tube are wheeled into position, one below the patient and the other above, until the centre point of the plate holder is in the beam of light, when the plate holder and the tube will be automatically centred. We have found that much time is saved if the development of the plates is carried out in a room adjacent to the theatre and communicating with it by means of a hatch, through which the plates may be passed and the developed films returned.

The injection of radiological contrast solutions into the biliary tract can irritate the mucosa and upset the sphincter mechanisms. The hydrosoluble iodine solutions are particularly liable to this irritative action and to disturb the tone of both the sphincters of Lütcken and Oddi. The liposoluble contrast materials, however, have been found experimentally to have no such effect on sphincteric tone (Feit, 1951). The contrast materials which have been used in this technique are Lipiodol 'F' and Viskiosol. Hess (1955), however, advises the use of a low concentration of the hydrosoluble Diodone, believing that the Lipiodol has too great a contrast and may obliterate the shadows of small stones.

FIG. 59.—Lyons Series No. 2534, hypotonia of the common duct. The graph shows a marked degree of hypotonia, the pressure taken in the common duct stabilized at 0 cm. of water. The cholangiogram shows a slightly dilated, tortuous common duct which is unduly angulated. The sphincter of Oddi is widely open. There is also a marked narrowing of the hepatic duct.

FIG. 60.—Newcastle Series No. 96, cholecystectomy and generalized hypotonia. The graph taken in the gall-bladder shows that the pressures are stabilized at 10 cm. of water. The cholangiogram shows an atonic gall-bladder, the common duct, barely visible overlying the spine, is narrow and much of the contrast material is in the duodenum.

In spite of the increasing perfection of intravenous cholangiography, we believe that in by far the greater number of cases it is necessary to take a cholangiogram during operation. In a series of 400 cases of intravenous cholangiography 166 were controlled per-operatively by manometry and radiography. In 73 cases the common duct showed no abnormality before operation, but at operation only 21 were found in fact to be normal functionally and a pre-operative intravenous cholangiogram will sometimes demonstrate a lesion, it more often indicates the necessity for further diagnostic measures—i.e., per-operative manometry and radiography. In the presence of a normal common duct the per-operative cholangiogram may be omitted, but never the manometric estimation of stabilized pressure. Finally the per-operative cholangiogram is essential in the great majority of cases.

FIG. 61.—Lyons Series No. 2560, post-operative stricture of the common duct. The graph shows the typical blockage curves and the cholangiogram complete obstruction of the common duct. Above the block the duct is dilated and there is also marked dilatation of the hepatic duct.

FIG. 62.—Lyons Series No. 2145, pseudo-cyst of the pancreas. The graph shows the blockage curves of an obstruction. The cholangiogram shows that the common duct is greatly narrowed in its pancreatic portion. The intramural portion of the duct is normal. The hepatic duct is dilated and there is a massive reflux into the hepatic ducts.

anatomically. It was concluded therefore that even with a normal pre-operative cholangiogram it is still necessary to carry out manometric control. It is, however, sometimes possible to arrive at an exact diagnosis by means of a pre-operative intravenous cholangiogram; for instance, from the series, 11 had demonstrable calculi, 1 had a compression of the common duct by chronic pancreatitis, and 1 showed a post-operative stricture. A dilatation of the common duct was found in 30 per cent of the cases, but this alone does not allow a precise diagnosis to be made. We have come to the conclusion that while

In order to explore completely the common duct and the whole of the pancreas, an adequate exposure is necessary, and it has been found that a modified Rio Branco (1912) incision is probably the best; it begins at the xiphisternum and follows the midline for a short distance, and then, deviating a little to the right, extends to just above the umbilicus. At this point it turns at right angles to cut the right rectus muscle transversely and then ascends obliquely to the 9th costal cartilage, running parallel with the intercostal nerves. Both skin and muscle are divided in this line. Hæmostasis having been secured, the

peritoneum is opened and the upper abdominal cavity thoroughly explored. The condition of the gall-bladder is noted, whether it is pathological or contains stones. The common duct is very carefully examined for dilatation, stones, or growth. Finally the pancreas is examined in its entirety. Any gastric or duodenal ulceration should be noted also.

In proceeding with the investigation the next step depends on the condition of the gall-bladder.

FIG. 63.—Lyons Series No. 2304, carcinoma of the pancreas. The cholangiogram shows a widely dilated common duct which is blocked at the junction between the pancreatic and suprapancreatic portions. The hepatic ducts are also widely dilated and there is a marked hepatic reflux.

If this organ is normal and there is no obvious lesion in the common duct then the pressure readings are taken through the gall-bladder. A straight cannula armed with a bayonet-pointed trocar is thrust through the fundus and tied into position. The first few readings are of little significance because the gall-bladder is merely filling and each stabilized pressure will be at a slightly higher level until the gall-bladder is full, when a series of stabilized pressures around the same level will be obtained. Having taken the pressure, the next step is to remove the pressure tubing from the cannula and substitute a 20-c.c. syringe full of lipiodol (fluid), the spot light is adjusted to illuminate the duct, the wound is covered with a large sterile towel, and the X-ray tube and plate holder are wheeled into position. The first exposure is made after the whole 20 c.c. of lipiodol have been injected. Three minutes later a second plate is exposed; this plate gives information concerning the evacuation of the gall-bladder. This completes the investigation and the cannula is removed and the hole in the gall-bladder wall repaired with a double row of sutures.

If the gall-bladder shows such pathological change as to necessitate its removal, then the cystic duct is intubated with a special cannula which is ligated in position. The cannula has two bends in it and the ligature should surround the second part. The

FIG. 64.—Lyons Series No. 2368, post-cholecystectomy syndrome, ampullary calculus. The graph shows the typical blockage curves. The cholangiogram shows a dilated and angulated common duct, the lower end of which is amputated and terminates in a concavity. There is massive hepatic reflux into widely dilated hepatic ducts.

stabilized pressures are then taken in precisely the same manner as before. Having ascertained the stabilized pressure within the common duct, the recording tube is removed and the syringe with lipiodol is attached. In this case only 10 c.c. of lipiodol are injected and an X-ray plate is taken. A second plate is taken three minutes later after the injection of another 10 c.c., and a third plate may be taken three minutes after this one. The investigation being completed, the cannula is removed and the cystic duct completely divided and ligated.

INTERPRETATION OF RESULTS

In a normal state the pressure curve descends regularly and is slightly concave. Sometimes small variations may be seen owing to respiratory movements. Much experimental work has been done to establish a normal pressure in man and animals. It is generally regarded that a pressure of between 8 cm. and 14 cm. of water is normal in the common duct (Kipp, 1936; Mallet-Guy, Jeanjean, and Marion, 1947). Factors which influence the biliary pressure are the secretion of bile by the liver, the tonicity of the sphincters, and the tonicity, elasticity, and contractility of the ducts. Any alteration in the tone of the biliary tract will be manifest in the pressure curve. Should the muscular wall of the tract have lost its tone and acts merely as an elastic membrane, then there will be a low pressure and a rapidly descending curve. If there is an obstruction to the outflow of bile a high pressure will develop, and if there is a complete obstruction each stabilized pressure will be higher than the one before. When the pressure is taken in the normal gall-bladder it is usually about 18 cm. of water (Crain and Walsh, 1931; Bengeret, Carroi, and Debouvrey, 1940).

The Normal Pressures.—It is quite common on a normal cholangiogram to see some reflux into the hepatic ducts, which is of no significance. The sphincter of Oddi is usually clearly seen at the lower end of the common duct as a distinct but not excessive narrowing. Sometimes even in normal cases there is a very short reflux along the duct of Wirsung (Mallet-Guy, Guillet, and Durrand, 1948). A normal gall-bladder is pear-shaped with an ovoid fundus. The body should not be indented by the surrounding viscera, but may show peristaltic waves. The cystic duct is filled when the gall-bladder evacuates and shows as a narrow sinuous canal joining the common duct (*Fig.* 51). In the normal state the common duct is about 3–4 mm. in width and may show peristaltic waves. In the first X-ray plate one may see the bifurcation of the common hepatic duct. On the second plate the gall-bladder image is the same size as before, but the common duct has diminished appreciably in width.

The stabilized pressure within the biliary system may be normal or below or above normal. A raised stabilized pressure indicates a state of hypertonia or mechanical obstruction. It was Oddi (1888) who first recognized a state of hypertonia of the biliary

FIG. 65.—Lyons Series No. 2088, tumour of the ampulla of Vater. The graph taken in the gall-bladder stabilized at 21 cm. of water. The cholangiogram shows a widely dilated common duct which ends irregularly transversely at the lower end; some contrast material has outlined an irregular channel through the obstruction.

FIG. 66.—Newcastle Series No. 21, tumour of the hepatic duct. The cholangiogram shows a blocked hepatic duct, the common duct is grossly angulated, the contrast material has passed freely into the duodenum.

system. He found that after cholecystectomy the common duct dilated, and he believed that this could only come about as a result of a spasm of the termination of the common duct—in fact a spasm of the hitherto unrecognized sphincter of the common duct which now bears his name. Hypertonia may be an essential, i.e., functional hypertonia or an organic hypertonia due to an obstructive lesion, or else a combination of the two.

The Hypertonic States.—In a state of hypertonia both the manometric and radiographic findings are quite clear. The pressure curve instead of falling

FIG. 67.—Lyons Series No. 2483, post-cholecystectomy syndrome, choledochlithiasis. The graph shows that the pressure curves within the common duct stabilized at 7 cm. of water. The cholangiogram shows quite clearly a filling defect which almost completely fills the duct; some of the contrast material however has passed the obstruction and entered the duodenum. The shape of the filling defect is characteristic of a stone. There is also a considerable degree of narrowing of the hepatic duct.

to about 15 cm. of water in a few seconds and then more slowly to 8–14 cm., remains comparatively elevated and descends in a step-like manner to perhaps 20–25 cm. of water, and it may take several revolutions of the drum to reach this level. In a complete or almost complete organic obstruction each succeeding stabilized pressure is higher than its predecessor, giving a pattern which is quite characteristic of a mechanical obstruction (*Fig.* 52). The cholangiogram shows a dilatation of the common duct up to double the normal diameter. There is a reflux of the contrast material along the hepatic ducts and the flow into the duodenum is minimal. The sphincteric portion of the duct is very narrow and long and is often not visible at all. Waves of peristalsis are frequently seen. Quite often there is reflux along the duct of Wirsung for a varying distance.

The pressure stabilizes at a higher pressure than normal in various conditions, such as the post-cholecystectomy syndrome (*Fig.* 53), lithiasis, and

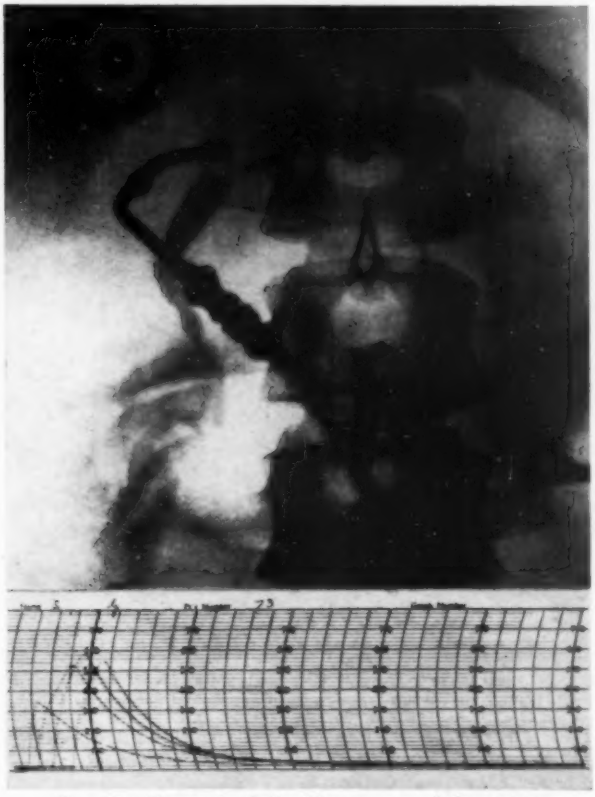

FIG. 68.—Newcastle Series No. 73, post-cholecystectomy syndrome, hypotonia of the sphincter of Oddi. The graph shows a common duct pressure stabilized at less than 2 cm. of water. The cholangiogram shows an angulated common duct with a widely open sphincter of Oddi.

chronic pancreatitis, as well as malignant disease involving the duct. Hypertonia may be classified as functional, organic, or organo-functional. It may affect the whole or part of the biliary tract. Commonly the hypertonia is limited to the sphincter of Oddi, in which case the common duct is dilated and there is an abnormal degree of hepatic reflux (*Fig.* 54). There is often a reflux along the duct of Wirsung as well. The end of the common duct shows one of several abnormalities, the sphincteric passage may be eccentric, it may end like the bottom of a test-tube, or it may be fusiform. A state of hypertonia (*Fig.* 55) isolated to the gall-bladder is comparatively rare and occurs in affections of the cystic duct, in which case the gall-bladder pressure may be up in the thirties or forties yet the common duct empties rapidly into the duodenum through an open sphincter.

When a hypertonia is diagnosed it is necessary to carry the diagnosis a stage further and decide whether the abnormal pressure is functional or organic or a combination of the two. The sphincter of Oddi is under the control of the sympathetic and the vagus nerves and the latter is the motor nerve (Ivy, 1930). In a case of functional hypertonia infiltration around the terminal vagal fibres with a local anæsthetic will

FIG. 69.—Lyons Series No. 2539, hypotonia of the sphincter of Oddi. The graph shows that the intraduct pressure stabilized at 2 cm. of water. The cholangiogram shows a widely-open sphincter of Oddi, a moderate reflux along the hepatic ducts, and a well-marked reflux along the duct of Wirsung.

abolish the spasm of the sphincter and lower the pressure. Should a reduction not take place then the cause of the hypertonia is organic, or if the reduction is small then it is organo-functional.

The Hypotonic States.—The pressure curve of vesicular hypotonia is quite characteristic (*Fig.* 56); the curve descends rapidly in the first ten seconds or so to a level below normal, and in less severe cases may resemble the curve of a normal common duct pressure. Radiologically the gall-bladder is distended, elongated, and often deformed by neighbouring viscera. Peristaltic waves are absent and the evacuation is variable and if, as usually, there is a common-duct hypotonia as well, the contrast material will flow down the common duct as it is injected. It must not, however, be assumed that this will be the case. A hypotonic common duct is usually dilated and evacuates passively through a widely open sphincter (*Fig.* 57). The hepatic ducts are dilated often up to two or three times their normal width. Sometimes, however, instead of a dilated duct an extremely narrow duct is found with rapid evacuation into the duodenum through a wide open sphincter (*Fig.* 58). It would appear that the first stage of a hypotonia of the common duct is one of a reduction in the calibre as though the wall of the common duct was contracting in an attempt to maintain a sufficient pressure in the face of an atonic sphincter, and it is only later that a secondary dilatation occurs. When the pressure is taken directly from the common duct the curves fall rapidly to a level lower than normal, to 5 cm. or less. In the cholangiogram the common duct appears to be elongated and either curved, angulated, or even sinuous in character (*Fig.* 59).

A lowered stabilized pressure indicates a state of hypotonia. Vesicular hypotonia has been recognized for some time, but it is only within recent years that hypotonia of the duct system has been diagnosed with certainty. Chiray and Pavel (1925) were perhaps the first to describe a state of hypotonia of the gall-bladder; Judd and Mann (1917), and Eisendrath and Dunlavy (1918), described a progressive fall in biliary pressure after a preliminary rise in patients who had their gall-bladder removed, and one of us (P. M.-G.) described a state of hypotonia of the sphincter of Oddi after cholecystectomy (Mallet-Guy, Marion, and Kess, 1944). Hypotonia may be essential (*Fig.* 60) or associated with other lesions of the biliary tract such as stones or a pancreatitis. It may be local, general, or dissociated.

Stenotic Conditions.—In stenotic conditions of the biliary tract the obstruction may be complete or incomplete, each giving different manometric and radiologic findings. In complete stenosis each stabilized pressure is higher than the one preceding (*Fig.* 61). If there is an obstructive jaundice the pressure will be above 30 cm. In fact it is not worthwhile carrying the stabilized pressures above this level because in the region of this pressure there is a reversal of function of the liver cells (*Fig.* 62). The radiological findings in such conditions are most informative: there is dilatation above the site of obstruction, which may be considerable, and the site and nature of the obstruction will be demonstrated. In complete obstruction the picture is one of an amputated duct. The form of termination of the duct gives a clear indication of the cause of the obstruction.

A common cause of biliary obstruction is carcinoma of the head of the pancreas, in which case the patient is nearly always jaundiced and the obstruction complete, with a stabilized pressure of about 30 cm. Radiologically the duct system is enormously dilated and the common duct is amputated at the level of the head of the pancreas and ends as an irregular cone or hemisphere, or as a straight line, but in each case the outline is irregular (*Fig.* 63). A stone can often cause symptoms indistinguishable from a carcinoma of the pancreas, but radiologically there is no mistaking a stone (*Fig.* 64). In carcinoma

the duct ends in a convex or nearly convex line, but in the case of a stone the duct ends in a concave line. A carcinoma of the ampulla of Vater also gives symptoms similar to a carcinoma of the head of the pancreas (*Fig.* 65). It is important to differentiate between these two conditions because the prognosis of carcinoma of the ampulla is much better than for a carcinoma of the pancreas. The common duct usually ends in an irregular cone at the level of the papilla, whereas a carcinoma of the pancreas obstructs higher up the duct. Tumours of the hepatic ducts are also a cause of jaundice and are seen on the cholangiograms as obstructions of the hepatic duct (*Fig.* 66) complete or incomplete: also one of the two main branches may be the site of a growth.

of fibrosis of the sphincter as well, in which case the pressure is not reduced to normal by vagal infiltration so that a sphincterotomy is indicated (*Fig.* 54).

A hypotonia of the sphincter is also the cause of failure (*Fig.* 68). It is often in these cases that there has been no relief at all from the primary operation and there has been a continuance of the original symptoms. This points to the conclusion that the hypotonia was present at the time of the first operation. A hypotonic state of the biliary tract is an indication for a right splanchnicectomy (*Fig.* 69).

Stenosis of the common duct is also a cause of trouble following cholecystectomy (*Fig.* 61). It may be due to injury of the duct at the time of the original operation, a co-existent chronic pancreatitis,

Table I.—THE CAUSES OF THE POST-CHOLECYSTECTOMY SYNDROME

	Lyons Series—58 Cases		*Newcastle Series—22 Cases*	
a. Morphological Changes :—				
Calculi	8		3	
Chronic pancreatitis	8		2	
Stricture	4		1	
Incomplete cholecystectomy	3		4	
Hepatitis	3		3	
Ampullary carcinoma	1			
Duodenal adhesions	1			
	28	(48 per cent)	13	(59 per cent)
b. Functional Changes :—				
Hypertonia	10		1	
Hypotonia	17		7	
	27	(47 per cent)	8	(36·5 per cent)
No obvious cause	3	(5 per cent)	1	(4·5 per cent)

The Post-cholecystectomy Syndrome.—The failure of cholecystectomy is a common occurrence which is often disregarded by the surgeon, recognized by the physician, battled with by the general practitioner, and must prove such a bitter disappointment to the patient. We have shown that at least 30 per cent of blind cholecystectomies do not cure the patient, and of these slightly less than one-half are so bad that the sufferers welcome the suggestion that another operation offers a chance of recovery. In the past when these cases have been explored surgeons have been disappointed to find morphological changes in only a small proportion of them. In our series definite morphological change—recurrent stone (*Fig.* 67), chronic pancreatitis, and stricture of the duct—only occurred in 30 per cent. The operation is difficult not to say hazardous, on account of the numerous and often dense adhesions which are encountered. In many cases the passage of recurrent hepatic stones was looked on as a cause for bouts of jaundice and pain. Since the use of manometric and radiographic control at operation for the post-cholecystectomy syndrome it has been possible to discover the underlying functional disturbance which is undoubtedly the cause of many of the failures after cholecystectomy.

The stabilized pressure may be high, normal, or low. A spasm of the sphincter of Oddi is frequently the cause of trouble following cholecystectomy, and we have found it to be present in about 20 per cent of the cases. In such cases we performed a low vagotomy. In some instances there is an element

or more rarely a tumour of the duct. In the latter case it is quite possible that the tumour existed at the time of the cholecystectomy and was the cause of the aggravation of symptoms which rendered the operation necessary.

A recurrent stone in the common duct is a not uncommon cause of post-cholecystectomy jaundice and pain. While undoubtedly a certain number of calculi are new formations, many more are stones which have been left behind at the previous operation and could have been demonstrated radiologically had a per-operative cholangiogram been taken.

A further cause of symptoms following cholecystectomy is chronic pancreatitis, which may have been present but unrecognized at the first operation. The condition is diagnosed by careful examination of the pancreas, radiological deformation of the common duct in its pancreatic portion, and frequently by a marked reflux along the duct of Wirsung in association with a hypotonia of the sphincter of Oddi. In these cases it is most probable that both the hypotonia and the reflux were present at the time of the cholecystectomy (*Table I*).

The mechanism of the biliary tract is particularly sensitive to functional disturbances, whether primary or secondary, disturbances which must not be overlooked if the surgeon is to guard against the all too frequent continuance or recurrence of symptoms after cholecystectomy. It is not enough to recognize only the morphological changes which may occur in the biliary tract, the alterations of function are equally important, and we have described here the most

precise and valuable methods of studying these two types of pathological change during operation.

CONCLUSIONS

In spite of the advances which have been made in the diagnosis of biliary tract disorders by such means as cholecystography, intravenous cholangiocystography, duodenal intubation, and its latest development, the chronovolumetric estimation of bile, the clinician is often left in considerable doubt as to the exact diagnosis of biliary tract disease. While any one or all of these methods will indicate that a disturbance of function exists, quite often its character remains obscure. In cases of obstruction, radiological examination before the operation, and visual and tactile examination at the time of operation, may fail to make clear the precise cause. By means of the technique described any alteration in biliary tract function is clearly revealed and steps may be taken to correct the abnormality, also the operator is enabled to make an exact morphological diagnosis and to ensure that no stones that could be removed are left in the duct system.

The technique has revealed that disturbances of biliary tract function are common occurrences and may be divided into hypotonic and hypertonic states. It has also demonstrated that these disturbances are frequently associated with gall-stones. By means of this technique it has been shown that the greater proportion of post-cholecystectomy syndromes are functional in origin, and it is believed that the functional abnormality frequently existed at the time of the original operation. Many of the remaining are due to morphological conditions overlooked at the primary operation, which could have been revealed by this technique.

It is the authors' view that the practice of per-operative manometry and radiology in every case of surgery of the biliary tract will give clear operative indications, which if carried out will reduce considerably the number of failures after operation, and its use in operation on post-cholecystectomy syndromes will lead to a high percentage of cures.

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HORMONES IN THE TREATMENT OF CANCER OF THE BREAST AND PROSTATE*

WITH SPECIAL REFERENCE TO THE ADRENAL GLAND

By L. N. PYRAH

DEPARTMENT OF UROLOGY, UNIVERSITY OF LEEDS, LEEDS GENERAL INFIRMARY, AND ST. JAMES'S HOSPITAL, LEEDS

It is now known that the adrenal, the pituitary, the gonads, the breast, and the prostate are very closely interdependent and that the interaction of one upon the other is brought about by the action of hormones. It had previously been believed that cancers of the breast and of the prostate were autonomous and uninfluenced by any hormonal or other known mechanisms within the body; work on animals in the laboratory and on human beings in the clinic and in the operating theatre, has shown that some malignant tumours of the breast and of the prostate may be induced by hormonal action and that the growth of such tumours may be stimulated or inhibited by an alteration of their hormonal environment—in other words, they are hormone-dependent. Most work has so far been done, and therefore most is known, concerning the relationship between œstrogens and mammary cancer. The presence of œstrogens in the body for a long time does not, however, in every woman lead to the development of mammary cancer. Further, in many malignant tumours there is no evidence of hormonal dependence, so that it would appear that factors other than hormones must be of aetiological importance. In human beings a hereditary factor seems to be present in certain carcinomata of the colon, and in some instances carcinoma of the breast has appeared to run in families. There is also the experimental work of Bittner (1936, 1945) on mice, in which he demonstrated, apparently conclusively, that in certain strains a transmissible milk factor or agent operates in the production of breast cancer through successive generations. It may be that œstrogen produces its results not as a primary aetiological agent but by acting as an intermediary in some mechanism (as yet not understood), which does not in every case lead to mammary cancer.

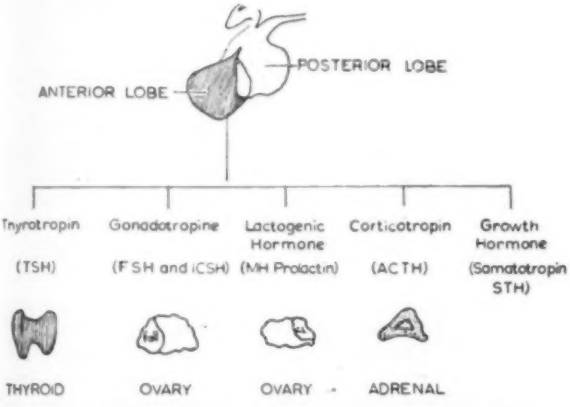


FIG. 70.—Scheme showing the principal hormones of the pituitary gland.

NORMAL MECHANISMS

Since, therefore, œstrogen is believed to be in many cases at least one factor in the cancer-producing mechanism, I shall refer to the place of œstrogen and its mode of formation within the ductless gland system. The principal hormones formed by the anterior lobe of the pituitary and their target organs are shown in *Fig.* 70. The thyroid stimulating hormone acts upon the thyroid gland to produce thyroxin; of the gonadotrophins, follicle-stimulating hormone (FSH) acts upon the ovarian follicle resulting in the production of œstrogen (which, in turn, as its concentration in the blood rises, retards the formation of FSH), and interstitial-cell stimulating hormone (ICSH) acts upon the interstitial cells (Leydig) of the testis resulting in the production of androgen (which, in turn, as its concentration in the blood rises, retards the formation of ICSH); luteinizing hormone (LH) assists in the formation of the corpus luteum; luteotropic hormone acts upon the corpus luteum to produce progesterone; corticotrophin (ACTH) acts upon the adrenal cortex (*Fig.* 71) to produce œstrogen and corticosteroids, including cortisone-like bodies; and growth hormone (somatotrophin, STH) promotes the normal growth of many tissues of the body.

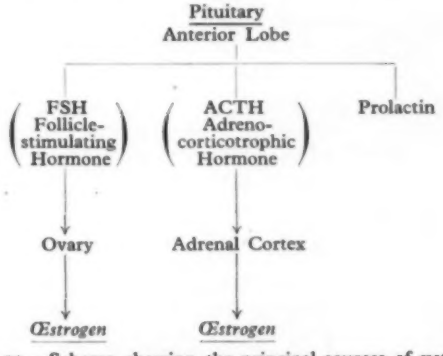


FIG. 71.—Scheme showing the principal sources of œstrogen production.

Œstrogen is produced not only in the ovarian follicle but also in the corpus luteum and in the placenta, and its output during reproductive life is regulated by a pituitary-ovarian balance; removal of the pituitary results in anatomical and physiological atrophy of the ovaries and abolishes the supply of œstrogen.

Œstrogen levels in the blood vary during the menstrual cycle and also at other periods during reproductive life.

* The Weild Lecture given before the Royal Faculty of Physicians and Surgeons of Glasgow on Dec. 7, 1955.

The Menstrual Cycle.—During the first twelve days of the menstrual cycle when the ovarian follicle gradually ripens under the influence of the follicle-stimulating hormone, the ovary secretes an increasing amount of œstrogen, as shown in the rising curve on the chart (*Fig.* 72). The secretion of the luteinizing hormone of the pituitary appears about the eighth day and increases thereafter until the thirteenth to the fifteenth day, when ovulation takes

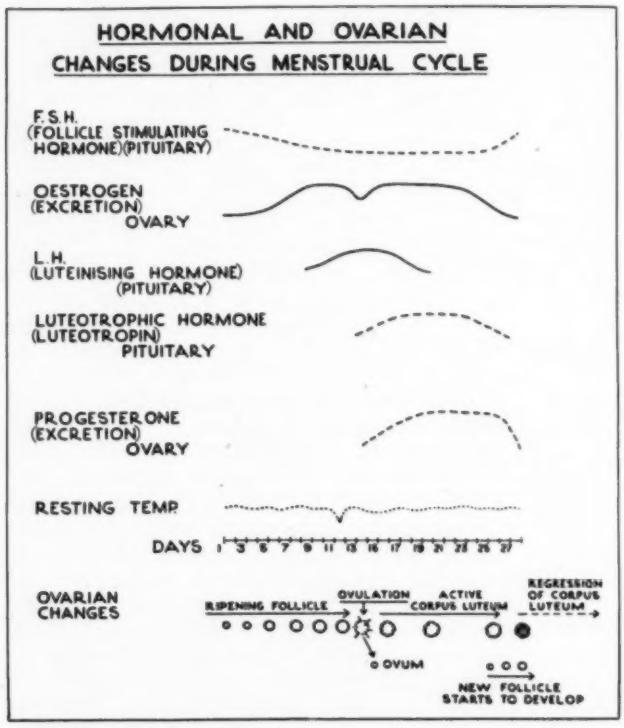


FIG. 72.—Hormonal changes during the menstrual cycle. The rise and fall of curves represent approximate quantitative rises and falls in the production of the hormones.

place. Luteotrophic hormone is produced by the pituitary from the thirteenth day onwards, producing progesterone in addition to œstrogen; progesterone is produced by the ovary from approximately the fourteenth day onwards, and its maximal production is achieved between the twentieth and the twenty-fifth day, and thereafter falls rapidly until the end of the menstrual cycle. In addition to producing progesterone, the corpus luteum also produces œstrogen; the corpus luteum remains active until the twenty-sixth day, after which it regresses and a new follicle starts to develop under the stimulus of the further formation of follicle-stimulating hormone.

During lactation the output of œstrogen from the ovaries is reduced to a negligible quantity. Removal of the ovaries does not entirely suppress the formation of œstrogen, and there is experimental evidence that the adrenals are then the source of the œstrogen. After the menopause, when the ovaries cease to respond to follicle-stimulating hormone, the adrenals may produce greater amounts of œstrogen than before the menopause.

It follows from this sequence of changes that women differ from one to another in the length of time in their reproductive lives during which they are subject to the stimulus of œstrogen. Women who have become pregnant repeatedly, have been subject to œstrogen for a considerably shorter time than women who have never had a pregnancy; women who have had the ovaries removed before the menopause have been subject to œstrogen for a shorter time than women who have not had that operation.

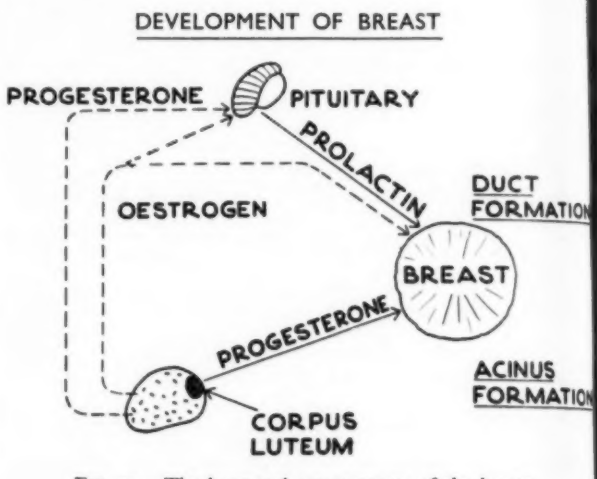


FIG. 73.—The hormonal arrangements of the breast.

Development of the Breast.—The development of the breast is closely linked with the action of œstrogen. The normal, mature breast consists of ducts and of acini, and these require different hormonal stimuli for their development (*Fig.* 73). The development of the ducts depends primarily upon the hormone prolactin derived from the anterior lobe of the pituitary under the stimulus of œstrogen; for the complete development of the ducts, œstrogen and prolactin act together. The development of the acini depends primarily upon progesterone, provided œstrogen is also present and provided the pituitary is intact.

MAMMARY CANCER AND ŒSTROGENS IN MICE

Experimental work on the animal has given us much fundamental knowledge about the carcinogenic properties of œstrogen and the conditions under which its effect is produced (Burrows and Horning, 1952). I will refer to three separate groups of facts, which have been learned from studies of mammary cancer in mice.

1. Œstrogen Withdrawal may lead to a Reduced Incidence of Breast Cancer.—Lathrop and Loeb (1916) showed that the removal of the ovaries in cancer-bearing strains of mice before the age of six months reduced the incidence of mammary cancer and caused it to appear at a later age than in non-oöphorectomized controls. Loeb (1919) showed that if the ovaries were removed at the age of three to five months, mammary cancer did not appear at all or only exceptionally; if they were removed at the age of five to seven months the incidence of cancer was notably diminished and the disease appeared later in life; if the ovaries were

removed at the age of eight to ten and a half months, cancer appeared as frequently as in the non-oöphorectomized controls. These findings, which applied in all strains which were used, suggested that if the stimulus of œstrogen was quantitatively reduced over a given time, there was a proportionate reduction in the incidence of cancer.

It has been similarly shown by Cori (1927) that the removal of the ovaries in female mice between the fifteenth and the twenty-second day of life prevented entirely the occurrence of breast cancer as against an incidence of 79 per cent in the controls; removal of the ovaries between the ages of two and six months considerably reduced the incidence of breast cancer though it did not entirely prevent it. Murray (1936) found that in certain strains of female mice which had a natural incidence of cancer, cessations of breeding and removal of the ovaries in animals approaching the period of declining reproductive power resulted in an increase in the expectation of life and in a reduction in the incidence of cancer, especially in the older age groups.

2. Œstrogen Stimulation may be followed by Breast Cancer.—If additional œstrogen is supplied to mice experimentally, proliferative changes in the breast may develop which are sometimes followed by simple tumours and by carcinomata. Many œstrogenic substances, natural and synthetic, have been tested experimentally and have been found to be carcinogenic in mice; such substances include œstrone (Lacassagne, 1932; Burrows, 1935), œstradiol (Gardner, Smith, Allen, and Strong, 1936), triphenyl-ethylene (Robson and Bonser, 1938), and stilbœstrol (Lacassagne, 1938).

Lacassagne (1932) produced mammary cancer within six months by the injection of œstrin into male mice belonging to a strain, the females of which had a high incidence of spontaneous mammary cancer. Burrows (1935) induced in the breast dilatation of the ducts with hyperplasia of their epithelial lining, sometimes with cyst formation, in male and female mice following the twice-weekly applications of a benzene solution of œstrin to the skin; in some cases adenomata and occasionally carcinomata developed. Bonser (1936) obtained similar results following the injection of œstrone into male mice of a high cancer strain; breast cancer developed in 3 of 23 mice so injected, while others showed acinar proliferation and dilatation of the ducts.

There is experimental evidence that there is a quantitative relationship between œstrogen and the induction of mammary cancer and also that age has a bearing on the carcinogenic action of œstrogens on the breast; Loeb, Suntzeff, Burns, and Schenken (1944) showed that when male mice between the ages of two and six weeks were given daily doses of œstrone, cancer was induced, but not when a similar dose was given to older mice.

Mammary cancer may occur in the male breast following œstrogen stimulation. Murray (1928), using a strain of mice in which cancer of the breast eventually developed in 80 per cent of the untreated breeding females but in none of the males, removed the testes from male mice between the ages of four and six weeks; mammary cancer followed in a proportion of the castrated males into which he implanted an ovary taken from a sister.

3. Œstrogen may be formed in the Body in the Absence of the Ovaries.—Woolley, Fekete, and Little (1939) showed that in mice of a cancer-bearing strain spayed the day after birth, the incidence of cancer was considerably less than in animals in which only one ovary had been removed, and very much less than in intact, unmated females of the same strain. They further showed that in some of the mice spayed the day after birth, the vagina, uterus, and breasts later recovered from their post-castration atrophy and there were irregular cycles of œstrus. It seemed, therefore, that in spite of the absence of the ovaries considerable amounts of œstrogen had been produced in later life. The adrenals, which were found to be enlarged and to contain yellowish nodules, were believed to be the source of the supply of the œstrogen (Fekete, Woolley, and Little, 1941). Gardner (1941) also showed that spayed mice later showed evidence of œstrogenic activity, such as changes in the vaginal and uterine epithelium and some of the animals developed adrenal tumours.

REDUCED OVARIAN ACTIVITY IN WOMEN

Before referring to the results of gonadectomy in women and in men for the treatment of breast cancer, I shall mention four investigations recorded in the literature which tend to show that the absence of the ovaries in women or a reduced ovarian functional activity may result in a reduced incidence of cancer.

1. Herrell (1937) reviewed 1906 records of women who were treated for carcinoma of the breast and found that in this group the ovaries had been removed for various causes in 1·5 per cent of the series. He also examined the records of 1011 women in a similar age group who did not have mammary cancer and he found that oöphorectomy had been performed for various causes in 15·4 per cent. He suggested, from this evidence, that oöphorectomy had had a preventive influence against mammary cancer.

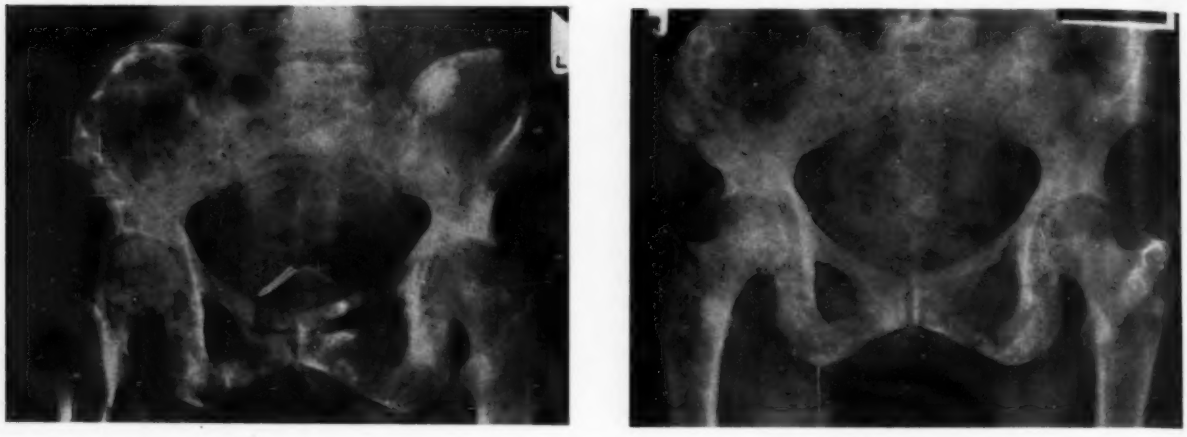
2. Horsley (1947) reported a series of cases in which radical mastectomy together with bilateral oöphorectomy had been used as the primary treatment for carcinoma of the breast. Of the cases so treated he found that a considerably higher percentage were free from recurrence after three years, and also after five years, than in a control series of patients treated by radical mastectomy alone.

3. Dargent (1949), from an investigation into the incidence of cancer in oöphorectomized women, concludes that it is rarer than in non-oöphorectomized women; he further considers that when cancer does occur in such patients it is of high malignancy.

4. Stocks (1953) reported a statistical analysis based on the incidence of mammary cancer in a series recorded by Smithers, Rigby-Jones, Dalton, and Payne (1952). He found that the mortality from mammary cancer after the age of 45 is greater amongst women who have never married; in women, the bearing of two or three children reduces the probability of its development by about one-fifth and the bearing of four or more children reduces it by about two-fifths. Multiple pregnancies thus have a protective effect.

HORMONAL TREATMENT OF MAMMARY CANCER

Considerations such as those which I have outlined constitute the factual and experimental background of the various hormonal treatments for advanced mammary cancer to which I shall now refer. The methods of treatment, all of which are indirect attacks upon the disease, are: the removal of the ovaries (or the testes in man), X-ray irradiation of the ovaries, treatment by testosterone or stilbœstrol, adrenalectomy, and hypophysectomy.



A B

FIG. 74.—Radiographs in *Case* 1. A, Pelvic bones and upper end of femora before bilateral oöphorectomy (March 20, 1954); B, Pelvic bones and upper end of femora 3 months after bilateral oöphorectomy) July 20, 1954).

Mammary Cancer and Gonadectomy in Women and Men.—

Oöphorectomy.—Although Schinzinger (1889), impressed by the atrophy of breast tissue which followed loss of ovarian function, advocated the removal of the ovaries in premenopausal women with mammary cancer, it was Sir George Beatson of Glasgow in 1896 who first noted a clinical improvement following removal of the ovaries for advanced mammary cancer in 2 of 3 cases, both being premenopausal. Following this work, beneficial results were recorded by other surgeons (Power, 1903; Waring, 1905; Clarke, 1905). Thomson (1902) analysed 80 cases in which oöphorectomy had been performed and found that there was a remission in 16 premenopausal and in 2 postmenopausal cases.

Lett (1905) collected a series of 99 cases with advanced mammary cancer in which oöphorectomy had been performed; there was an objective improvement in 22 of 75 patients in the premenopausal age group but in only 1 case of the 24 postmenopausal cases. In the series reported by Adair, Treves, Farrow, and Scharnagel (1945), and by Sicard (1947) a number of cases, mostly premenopausal, showed regression after oöphorectomy; the period of improvement was relatively short, usually from 6 to 12 months. In some cases, as in that of Raven (1950), longer remissions have been found.

Although after the publication of Lett's series in 1905 relatively few cases of oöphorectomy were recorded, probably because of the uncertainty of the results and the short period of regression, in recent years there has been a revival of interest in the operation, especially in view of its relationship to adrenalectomy. Pearson, West, Li, MacLean, and Treves (1955) have recently reported objective remissions averaging nine months in 44 per cent of 75 premenopausal women suffering from carcinoma of the breast with metastases, and only 10 per cent of objective remissions in 21 postmenopausal women; they found that the histological picture of the cancer was not helpful in predicting a favourable response; they recorded regression of metastases in the lungs, the bones, the skin, the liver, the peritoneum, the lymph-glands, and the central nervous system, as well as a shrinkage of the primary growth.

I have collected a series of 18 cases of bilateral oöphorectomy for advanced mammary cancer in premenopausal women done by myself and by two surgical colleagues. In 7 cases there was a response, usually of short duration, but longer in 3 cases. One case will serve as an example.

Case 1.—A woman, M. J., aged 46, had had a radical mastectomy for carcinoma in 1951. During the autumn of 1953 she developed skeletal metastases. On admission to hospital in March, 1954, she was almost moribund and was unfit for adrenalectomy. She had metastases in the ribs, the pelvic bones (*Fig.* 74 A), and the lungs.

OPERATIONS.—Bilateral oöphorectomy was performed on March 29, 1954. She made a spectacular recovery with recalcification of the skeleton and disappearance of the osseous metastases (*Fig.* 74 B). She regained her health and mobility and put on weight. So impressive was the improvement that bilateral adrenalectomy was performed ten months later (Jan. 31, 1955). She is still quite fit and active, and doing her housework one year ten months after oöphorectomy.

Orchidectomy.—In the male, Farrow and Adair (1942) recorded regression following orchidectomy in a case of metastatic mammary cancer, and Treves (1949) similarly noted remission in 3 of 6 cases.

Irradiation of the Ovaries.—The ovaries have been attacked by X-ray irradiation in an attempt to destroy œstrogen. De Courmelles (1905) first suggested irradiation of the ovaries as a treatment for mammary cancer as an alternative to oöphorectomy. Dresser (1936) reported regression of metastases following ovarian irradiation in 9 of 30 premenopausal women, Taylor (1939) noted improvement in 20 of 50 cases, and Ritvo and Paterson (1944) reported regression of skeletal metastases following ovarian

irradiation. Adair and others (1945) found improvement in 47 of 304 premenopausal patients. Douglas (1952) found improvement in 36 of 175 patients, of whom only 2 were postmenopausal; she aimed to deliver a dose of 700 to 800 r to the ovaries over a period of one week, though in some cases the dose was delivered as a single treatment; no correlation was found between the degree of the response and the site of the metastases, good results being seen in skin nodules and in metastases in the glands, the lungs, and the bones. The duration of the response following ovarian irradiation is usually only a few months, though regressions of two to three years have been noted (Dresser, 1936).

Table I.—Results in Treatment of Cancer of the Breast by Testosterone and Œstrogen in Various Series

Reference	Total Cases	Objective Improvement		Remarks
		No.	Per cent	
Testosterone				
Adair and Herrmann, 1946	11	4	36	Premenopausal
Adair and others, 1949	48	9	19	Bone metastasis
	54	8	15	Extraskeletal metastasis
A.M.A. Council on Pharmacy and Chemistry, 1949	82	15	18	Bone metastasis
	77	15	20	Extraskeletal metastasis
Segaloff, 1952	48	13	27	
Douglas, 1952	30	8	26	
Pearson and others, 1955	54		13	10 mth. premenopausal
	113		20	8 mth. postmenopausal
Peters, 1955	282	85	30	10 mth.
Pyrah, 1955	29	5	17	Premenopausal
	36	7	19	Postmenopausal
Œstrogen				
Ellis and others, 1944	100	14	14	Age less than 60 yr.
	68	27	39	Age over 60 yr.
Adair and others, 1949	35	8	23	
A.M.A. Council on Pharmacy and Chemistry, 1949	144	36	25	Postmenopausal
Douglas, 1952	322	98	30	Majority postmenopausal
Pearson and others, 1954	76		32	13·5 mth.
Peters, 1955	83	35	42	11·5 mth.
Pyrah, 1955	9			Premenopausal
	61	17	28	Postmenopausal

Testosterone.—Testosterone has been given for the treatment of metastatic mammary cancer with the object of neutralizing œstrogens; there is experimental evidence of a direct antagonism between œstrogen and testosterone. Lipschutz, Vargas, and Ruz (1939) showed that when the monobenzoate ester of œstradiol, the administration of which usually leads to the development of uterine fibroids, was given to oöphorectomized guinea-pigs along with testosterone, in the proportion of 1 to 22 or more, either no fibroids or only very small ones resulted. In premenopausal women, testosterone brings about an artificial menopause and might, therefore, be expected to act in the same way as oöphorectomy; it also causes an inhibition of the gonadotrophic hormones of the pituitary and this may produce an indirect effect on the breast cells (Moore and Price, 1932).

Testosterone was first used by Loeser (1938 a, b), who reported improvement in 2 cases, and by Ulrich (1939). It is given as testosterone propionate three times weekly in three-weekly intramuscular injections of 50–100 mg.; if a response occurs a 400–600 mg. pellet may be buried in the subcutaneous fat. Alternatively 50 mg. of methyl testosterone may be administered as sublingual pellets. Symptomatic relief is frequently induced in three weeks and is accompanied by a feeling of well-being, an improved appetite, and relief of pain: such a temporary subjective response has occurred in 50 to 60 per cent of reported cases, but this cannot necessarily be taken as a criterion of objective response, which only occurs in about one-fifth of the patients' treatment.

Table I shows the favourable responses obtained in a number of series of cases treated with testosterone. A short series from my own hospital shows that a response may be obtained in premenopausal as well as in postmenopausal cases. Peters (1955), in a large series of cases treated in Toronto General Hospital, found that in the premenopausal group treatment by androgen was less effective than treatment by œstrogen, whereas in the postmenopausal group androgens and œstrogens were equally effective.

Œstrogens.—Irrational as it may seem, since stimulation by œstrogens in certain animals gives rise to mammary cancer, some patients, especially postmenopausal, with metastatic mammary cancer, derive benefit from the administration of œstrogens; the mechanism by which this result is achieved is unknown. Zondek (1936) pointed out that such treatment would be likely to bring about an inhibition of the gonadotrophic and growth hormones of the pituitary which would result in a medical castration as well as in growth restraint. On the other hand, as Douglas (1952) points out, castration could not be regarded as complete with an œstrogen in the circulating blood-stream. It may be that the œstrogens have some direct action on the cancer cells.

Haddow, Watkinson, and Paterson (1944), who were the first to show that treatment by œstrogens could produce a remission in metastatic mammary cancer, reported improvement in 26·5 per cent of

204 patients treated with stilbœstrol for periods of one to nine months; relapse eventually took place. Œdema, gastric disturbances, vomiting, vaginal bleeding, and pigmentation of the areola and of the axilla were common complicating symptoms. The best results were obtained in postmenopausal women, though a response was found in some premenopausal women.

The results of treatment by stilbœstrol in several series of cases are shown in *Table I*. A series of cases from my own hospital showed a response in 17 of 71 cases treated by stilbœstrol; generally speaking the response was of short duration. Responses have been found in patients with skeletal as well as soft-tissue metastases.

Adrenalectomy for Metastasizing Mammary Cancer.—It was Professor Charles Huggins (1951, 1952 a, b), of the Billings Hospital, Chicago, and his co-workers, who, from a consideration of the available pathological and experimental evidence bearing upon hormone-dependent tumours, concluded that in certain cancers of the breast and of the prostate in which hormonal deprivation or therapy had resulted first in a regression of the growth and later in a relapse, there may have been a further build-up of a cancer-controlling substance within the adrenal gland. These workers, therefore, carried out bilateral adrenalectomy (usually with gonadectomy) in cases of advanced mammary and prostatic cancer with metastases in order to achieve the maximum reduction of circulating œstrogen or androgen. In some of the cases treated in this way they showed that a major remission of the cancer had been obtained.

Following the work of Huggins on cancer of the breast and of the prostate, two other considerations have arisen in connexion with the operation of bilateral adrenalectomy for carcinoma. Firstly, will adrenalectomy influence cancer in sites other than the breast and the prostate? Secondly, will cortisone alone inhibit cancer of the breast and prostate?

Miscellaneous Tumours treated by Adrenalectomy.—Pearson, Whitmore, West, Farrow, and Randall (1953) reported the results of adrenalectomy in 9 patients suffering from carcinoma of the cervix, carcinoma of the body of the uterus, carcinoma of the ovary, sarcoma of the uterus, malignant melanoma, acute leukæmia, and adenocarcinoma of the cæcum; no significant alteration in tumour growth was found in any of these patients. Taylor, Li, Eckles, Slaughter, and McDonald (1953) referred to 1 case of cancer of the ovary, and Cade (1954) to 2 cases of malignant melanoma, for which bilateral adrenalectomy had been performed without response.

Cortisone Treatment for Metastatic Cancer.—Cortisone inhibits the secretion of ACTH by the pituitary gland and in doses of 50 mg. daily it causes atrophy of the adrenal cortex and also a fall in the level of the 17-ketosteroids as after adrenalectomy (Birke, Franksson, and Plantin, 1954). Some workers have therefore treated patients who had mammary and prostatic carcinomatous metastases with cortisone in the hope of obtaining a remission, which might render surgical adrenalectomy unnecessary.

Leadbetter, Ganem, and Solomon (1952) treated 5 patients who had prostatic cancer with osseous metastases causing severe pain, with 100 mg. of cortisone daily; 2 patients were "dramatically relieved, one for three months and one for four months". In 2 other patients with advanced prostatic cancer complicated by severe purpura, cortisone gave dramatic relief to this symptom. Harrison, Thorn, and Jenkins (1952, 1953) found no objective remissions in 9 patients with reactivated prostatic cancer who were treated with cortisone in doses of 25 to 37 mg. daily for periods of one to three months; there was a reduction of the 17-ketosteroids in the urine. Many patients experienced a sense of well-being and partial relief of pain. Taylor and others (1953) treated 11 patients with metastatic mammary cancer with cortisone with no benefit and Segaloff, Carabasi, Horwitt, Schlosser, and Murison (1954) found subjective but no objective improvement in 11 patients with metastatic mammary cancer similarly treated. Cade (1954) reported 6 cases of advanced mammary cancer treated with cortisone with no beneficial effects.

Pearson and others (1955) treated 53 cases of mammary cancer with cortisone alone; in 14 cases in the group, consisting of patients of all ages, there were 14 per cent of remissions (duration not stated) using cortisone in doses of 50–75 mg. daily; in 39 cases of all ages using doses of 200–400 mg. of cortisone daily there was a 31 per cent incidence of objective remissions averaging three months. The results included shrinkage of a sloughing growth of the breast and improvement of pulmonary metastases.

Apart from the cases reported by Pearson and others (1955) some of whose cases had short remissions, the results of treatment by cortisone alone have been mostly subjective, including relief of pain, a feeling of well-being, and some improvement of general health. There is little to suggest that such treatment should replace the surgical removal of the gonads and the adrenals.

PRESENT SERIES

I have carried out between April, 1953, and November, 1955, bilateral adrenalectomy with oöphorectomy (or orchidectomy) in a series of 53 patients with advanced mammary cancer. A small number of cases which were referred for operation were rejected because of advanced malignant cachexia or senile changes. Many of the patients have been so ill that major surgery would appear to have been contra-indicated. Most of the patients, however, have survived their operation and many have obtained a major remission. Huggins has emphasized repeatedly in his writings (Huggins and Dao, 1953) that the most favourable response has been found in those cases in which the growth had an adenomatous or an alveolar structure and that little or no response occurred in those with anaplastic growths; other workers have disputed this finding. In the present series no preliminary selection was made on account of such histological differences.

PRE-OPERATIVE INVESTIGATION

Pre-operatively, clinical examination was made for evidence of metastases, and radiographs were made of the chest and the bones. A blood-count

was done, and the blood-sugar, the serum acid and alkaline phosphatase, the serum calcium and phosphorus, and the blood electrolytes were estimated and also the urinary 17-ketosteroids; in some cases the urinary calcium per twenty-four-hour period on an ordinary ward diet and in a few cases on measured low-calcium diet was also estimated. Blood transfusion was given pre-operatively in anæmic cases. In cases with pleural effusion resulting from pulmonary metastases, with consequent respiratory embarrassment, one or more aspirations have been done pre-operatively.

SUBSTITUTION THERAPY WITH BILATERAL ADRENALECTOMY

Cortisone substitution therapy is necessary for the maintenance of life after adrenalectomy. Although Huggins and Scott (1945) had carried out bilateral adrenalectomy for metastatic cancer in 4 cases, using only the adrenocortical extract then available (3 of their cases being fatal soon after operation), it was not until cortisone became available that the operation could be performed with safety.

Cortisone Acetate is generally used for substitution therapy. A reserve of cortisone must be built up in the body before operation, and, since more of it is needed in the days immediately succeeding the operation (because of stress) than is needed normally, large pre-operative doses are needed. My earlier substitution routine was based on that recommended by Huggins and Bergenstal (1951), but after the publication of my first 22 cases (Pyrah and Smiddy, 1954) 2 patients, apparently reasonably fit, died without apparent cause a few hours after bilateral adrenalectomy and oöphorectomy. Fergusson (1954) had a similar experience, and suggested that the absorption of cortisone given orally, using different preparations, might not be entirely regular. The dosage, therefore, has been slightly increased in the immediate pre- and post-operative period. Deoxycortone acetate (DOCA) is given for some days. My present routine is given below :—

Day of Operation minus Two:—

Cortisone acetate	50 mg. 6-hourly intramuscularly
Deoxycortone acetate	3 mg. intramuscularly
Sodium chloride	3 g. by mouth

Day of Operation minus One:—

Cortisone acetate	50 mg. 6-hourly intramuscularly
Deoxycortone acetate	3 mg. intramuscularly
Sodium chloride	3 g. by mouth

Day of Operation:—

Cortisone acetate	200 mg. an hour before operation and
	50 mg. 4-hourly intramuscularly
Deoxycortone acetate	5 mg. intramuscularly

First Post-operative Day:—

Cortisone acetate	50 mg. 6-hourly intramuscularly
Deoxycortone acetate	5 mg. intramuscularly
Sodium chloride	3 g. by mouth

Second Post-operative Day:—

Cortisone acetate	50 mg. 6-hourly intramuscularly
Deoxycortone acetate	3 mg. intramuscularly
Sodium chloride	3 g. by mouth

Post-operative Days Three to Six:—

Cortisone acetate	50 mg. 12-hourly by mouth
Deoxycortone acetate	3 mg. intramuscularly
Sodium chloride	3 g. by mouth

After Sixth Post-operative Day:—

Cortisone acetate	25 mg. by mouth twice daily

The use of the pellet of DOCA (300 mg.), which was formerly implanted subcutaneously some days after operation, has been abandoned. Sodium chloride is given in capsules of 3 g. daily for the two pre-operative days and for the first six post-operative days. No laboratory test exists which will indicate a normal corticoid state, but a sense of well-being after operation, with a return of physical strength and energy, sometimes amounting to euphoria, together with a normal appetite, indicates a correct assessment of the dose. Conversely, a feeling of general weakness, lassitude, and listlessness, especially when associated with a soft, hypotensive, rather rapid pulse, normally indicates the need for a higher dosage of cortisone.

The clinical effect of complete cortisone withdrawal from an adrenalectomized patient was seen by Pearson and others (1953), who withdrew it in an attempt to maintain life without steroid hormone administration. Within twenty-four hours of the withdrawal the patient experienced general malaise, weakness, and loss of appetite; in a further twenty-four hours the weakness was profound, the patient being unable to leave her bed, and experiencing giddiness when in the upright position. At seventy-two hours nausea, vomiting, diarrhœa, and stupor followed; the skin became cold and dry and the pulse soft and hypotensive. There was a fall in the serum sodium and in the daily output of urine and an increase in body-weight resulting from water retention; there was no excessive loss of sodium in the urine. The clinical and biochemical changes were quickly reversed following the administration of cortisone.

Hydrocortisone.—Cortisone acetate cannot be given intravenously in cases of acute cortisone deficiency but hydrocortisone fulfils this need and is an adequate substitute for cortisone and should be available to the surgeon for use in emergency; even intramuscular cortisone may not be absorbed rapidly enough in a crisis. Hydrocortisone is available in solution containing 50 per cent of alcohol and may be given slowly in doses of 10 mg. in 500 ml. of normal saline.

Fluoro-hydrocortisone.—Certain adrenal steroids can be made more active by the incorporation of a halogen atom into the 9-alpha position (Fried and Sabo, 1954); of the possible halogen derivatives, the fluoro-compounds are the most potent. In the new compound, 9-alpha-fluoro-hydrocortisone, the sodium-retaining activity is especially increased (Liddle, Pecket, and Bartter, 1954); this compound

may be given by mouth in doses of 0·5–1·0 mg. in twenty-four hours. Preliminary tests using 9-alpha-fluoro-hydrocortisone, from the very small amount so far available, have been made with a view to seeing if this substance can be used to replace cortisone; in adrenal insufficiency 0·5 mg. of fluoro-hydrocortisone acetate has a much greater sodium-retaining action than 50 mg. of cortisone acetate (Garrod,

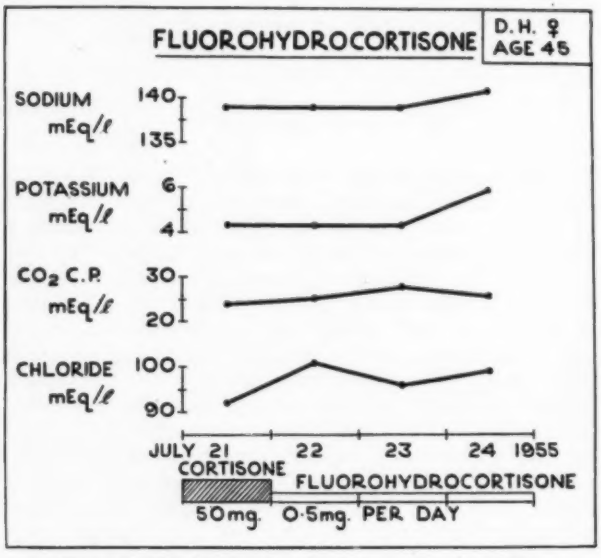


FIG. 75.—Blood electrolyte levels in a case in which 9-alpha-fluoro-hydrocortisone was substituted for cortisone for three days. No significant change in the levels was noted.

Nabarro, Pawan, and Walker, 1955), though clinically the patient may not be so well as when cortisone is given. In the occasional case in which the administration of cortisone acetate alone is followed by difficulty with the electrolyte balance, it seems possible that a combination of small doses of 9-alpha-fluoro-hydrocortisone with 20 to 25 mg. of cortisone acetate per day, all given by mouth, may obviate the need for injections of deoxycortone trimethyl acetate (Garrod and others, 1955). I have used fluoro-hydrocortisone on 2 patients in an attempt to replace cortisone acetate after adrenalectomy, using doses of 0·5 mg.; although there was no disturbance of the blood electrolyte pattern during the three days of its use (*Fig.* 75), both patients felt a little drowsy and faint and later developed nausea and vomiting, and the use of cortisone acetate had to be resumed.

Operative Removal of the Adrenal Glands

While the most direct operative route to the adrenal gland for the removal of tumours is either a transthoracic approach across the bed of the resected tenth rib, incising the diaphragm, or through an incision over the tenth or eleventh rib which is then resected and the pleura displaced upwards, in very ill patients with extensive metastatic carcinoma, and especially in those with pulmonary and pleural metastases, it is desirable to avoid a deliberate opening of the pleural cavity whenever possible. In the removal of the adrenals for the cases under consideration my own preference has been for the postero-lateral approach through the bed of the resected twelfth rib; a very satisfactory exposure is provided, though in stout patients the right adrenal gland may lie in a deep cavity; removal of the left gland is much easier. When the patient has been reasonably fit I have removed both adrenals and the ovaries at one operation through three incisions (23 cases), but when patients have been gravely ill, and especially when they have thoracic metastases, I have removed the right adrenal, with or without the ovaries, at a

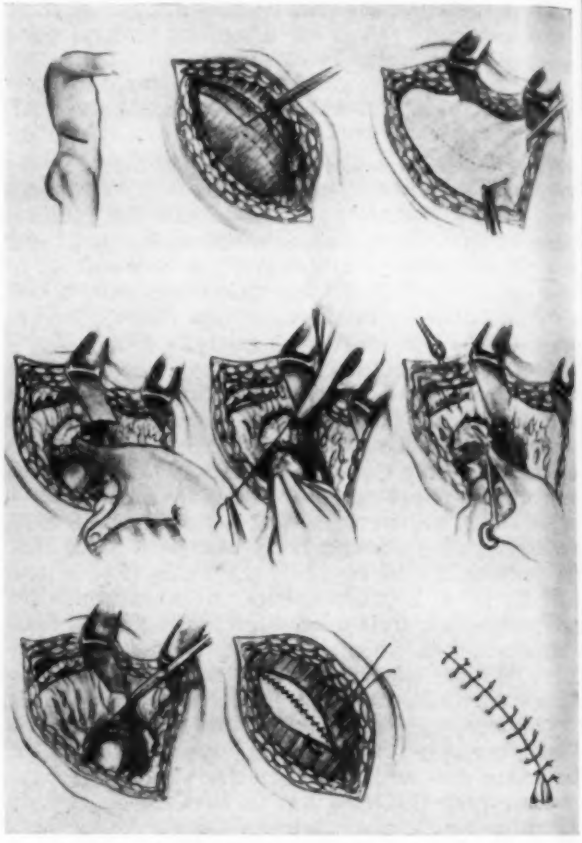


FIG. 76.—Schematic drawings to illustrate the operation of right-sided adrenalectomy.

first operation, and the left adrenal ten days later (30 cases).

Some surgeons have advocated a posterior approach and also a transperitoneal approach.

Posterolateral Adrenalectomy.—An intravenous drip of 5 per cent glucose in normal saline is set up before operation. Anæsthesia is induced with intravenous thiopentone; intratracheal gas and oxygen is then given through a cuffed tube and tubocurarine chloride given as a relaxant. A careful watch is kept on the blood-pressure, since it may fall during the operation, especially after the removal of the second adrenal, when noradrenaline may be used; severe falls in pressure in my experience are uncommon.

The patient is placed on her side in the kidney position, the loin being opened up either by raising the kidney bridge or lowering the head and foot of the operating table. It is sometimes an advantage to tilt the patient from the strict lateral position into a slight, semi-prone position, since this allows the easier removal of the twelfth rib close to the vertebral

column. An oblique incision over the twelfth rib as for the exposure of the kidney is made and is carried downwards and forwards for some inches (*Fig.* 76). The twelfth rib is resected subperiosteally, the incision deepened through its bed, and the lumbar muscles in front of it divided in the line of the incision. Sometimes the twelfth rib is very soft and may be crushed instead of being cleanly divided during its removal; in such cases microscopy has sometimes shown it to be infiltrated with cancer (*Fig.* 77) even when the radiological appearances had not suggested any such abnormality. The lower edge of the pleura as it passes horizontally across the upper part of the bed of the twelfth rib is defined and is displaced upwards; it may bulge from the presence of a pleural effusion. If the pleural cavity is inadvertently opened, it is repaired immediately, the delicate membrane being reinforced with muscle and the anæsthetist fully expanding the lung. The fascia of Gerota is incised and the perinephric fat separated from the upper half of the

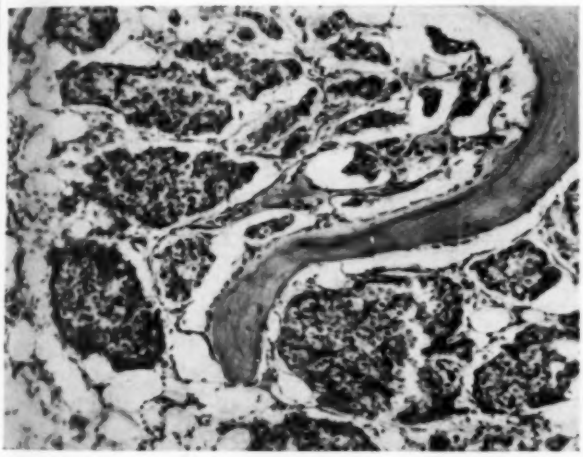


FIG. 77.—Metastatic mammary cancer in a rib found on histological examination. The radiographs did not suggest the presence of cancer. (× 240.)

kidney, which is then freed sufficiently to release its areolar attachment to the adrenal; the kidney is then displaced downwards in the wound and retained in that position first by the surgeon's hand and later by an egg-whisk type of retractor held by an assistant. At this stage, specially long instruments, including a finely-toothed dissecting forceps, thin, blunt-pointed, angled scissors, a long malleable lamp, and insulated diathermy hæmostatic forceps of different lengths, as well as a graded series of right-angled retractors of different sizes, are of great value during the subsequent dissection; the cautious use of the index finger is helpful. The lower border of the gland usually comes into view first and is recognized by its bright, orange-yellow colour. The fatty capsule surrounding the gland is dissected away or portions of it removed piecemeal, care being taken neither to tear the adrenal cortex, which results in an ooze of blood, nor to leave small processes of gland behind in the fat. The anterior and the posterior surfaces of the gland are freed first. The upper pole is closely related to the posterior surface of the liver and connected to it by areolar tissue which usually contains some vessels and these are sealed by diathermy before they are divided. Owing to its friability, forceps cannot be applied to the gland itself to be used for retraction, since they cut through and result in troublesome hæmorrhage; forceps may, however, be usefully applied to the adventitious tissue around the gland. The medial surface of the gland is closely applied to the inferior

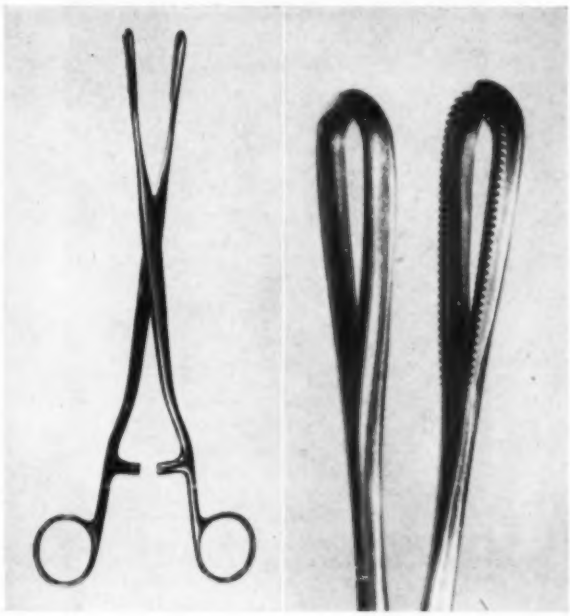


FIG. 78.—Ring forceps, 24 cm. long, with oval fenestrated ends and transverse groovings, suitable for seizing the inferior vena cava.

vena cava, to which it is connected by areolar tissue and by the short, stout adrenal vein which enters the gland on the medial part of its deep or anterior surface; sometimes there is an accessory adrenal vein going to the cava which must be recognized and ligated. The adrenal artery enters the hilum of the gland from beneath the vena cava and there may be an accessory artery, a branch of the renal artery. The vessels are secured by a long, curved forceps, the gland cut away, and the vessels ligatured. A hot, gauze pack pressed into the cavity will check oozing. Even with great care the adrenal vein may tear at its junction with the inferior vena cava; I have found that this little accident is most expeditiously dealt with by quickly mopping away the blood, and in the field thus rendered temporarily visible, seizing the wall of the cava at the bleeding point with a pair of sponge-holding forceps, the oval ends of which have transverse grooves (*Fig.* 78). The blunted end of the sponge forceps allows a firm ligature to be tied around the bleeding vessel.

The left adrenal is usually separated readily from the upper pole of the kidney; the head of the gland is closely related to the summit of the upper pole and the tapering body to the medial surface of the upper third of the kidney. The adrenal is related anteriorly to the splenic artery, though that structure is not usually in danger during the dissection. The lower pole is usually in close relation to the upper part of the vascular pedicle of the kidney, which is therefore

liable to injury and must be defined to enable the whole of the glandular tissue to be removed. The vascular pedicle of the adrenal on the left side is considerably longer and can be more readily demonstrated for ligature than that on the right; the left adrenal usually joins the left inferior phrenic vein.

FIG. 79.—Massive carcinomatous invasion of the left adrenal gland. The cortex and the medulla were infiltrated with cancer.

In 18 cases one or both adrenals were found to be infiltrated by cancer, either by small or large deposits (*Figs.* 79, 80), often causing the gland to be two or three times its normal size and more firm and rigid in consistency; such glands are usually easier to remove than the normal adrenal. Rarely, extensive hepatic and adrenal metastases infiltrating the parietes may render the removal of the adrenal impossible; occasionally both glands may be destroyed by cancer. Cade (1954) referred to a remarkable case under the care of Abrahams and Cox in which multiple bilateral pulmonary metastases underwent spontaneous disappearance with the simultaneous development of an Addisonian state; the condition was believed to be the result of the destruction of the adrenal cortex on both sides, since the patient's Addisonian state was promptly relieved by the administration of cortisone.

A search should be made at operation for accessory adrenals in the perinephric fat.

Bilateral posterior adrenalectomy: Some surgeons prefer the posterior approach with the patient flat on the face and the two ends of the operating table lowered. An oblique incision is made over the right twelfth rib and is prolonged outwards; the twelfth rib is resected. The operation then proceeds as in the posterolateral approach. The left adrenal is removed through a similar incision on the left side. Alternatively two surgeons can operate on the two sides simultaneously. Although I have no experience of this approach, it would appear to allow less room for manipulation and for the dissection of the friable and vascular adrenal glands than does the posterolateral approach.

Transperitoneal Adrenalectomy.—Aird and Helman (1955) have used this approach in 12 cases. An oblique incision is made, a hand's breadth below and parallel with the right costal margin, starting from a point just outside the lateral border of the right rectus muscle and carried upwards and to the left, to meet the left costal margin. The right rectus muscle and its sheath and also the linea alba, and the left rectus sheath and muscle are divided in the line of the incision. The peritoneal cavity is opened.

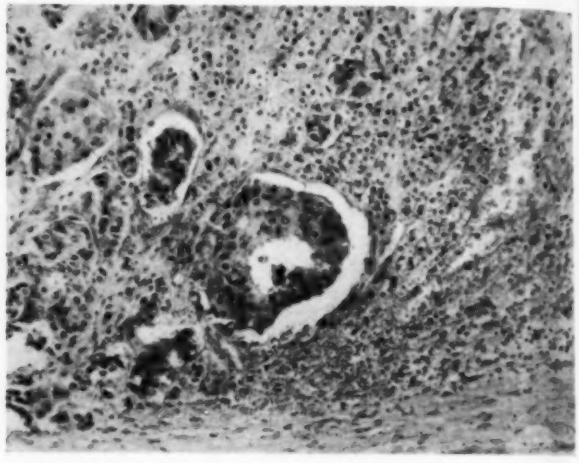


FIG. 80.—Microscopic invasion of the adrenal cortex by cancer. (× 137·5.)

The peritoneum of the posterior layer of the left lieno-renal ligament is incised, and the spleen, together with the tail of the pancreas, is mobilized and lifted forwards thus exposing the kidney covered by its capsule; the left adrenal is exposed after dividing the perinephric fascia. On the right side the liver may have to be partly mobilized by dividing the falciform and the right triangular ligaments; the upper pole of the right kidney is then drawn downwards by the surgeon's fingers thus enabling a small area of the peritoneum of the hepato-renal pouch to be excised after which the adrenal gland comes into view.

GONADECTOMY

The ovaries are removed through a middle-line subumbilical incision. On many occasions they have been involved in growth. The testes are eviscerated through an incision in the middle line of the scrotum.

POST-OPERATIVE PERIOD

In patients who have been reasonably fit before operation the procedure has been well borne and convalescence rapid; early movement and ambulation have been encouraged. In the more ill patients with generalized spread of the disease convalescence has been slower, and in those with extensive osseous metastases in the legs, pelvis, and vertebræ movement out of bed has been delayed until recalcification has been shown radiologically to be taking place, because of the danger of pathological fractures. Very striking has been the early and dramatic relief of pain, especially in the cases which subsequently have a regression; but even in less successful cases pain is

often relieved. There is also a considerable subjective improvement, almost with euphoria, and there is early improvement of the appetite and a desire for activity. It is necessary to keep a daily watch on the serum sodium and potassium levels and the intake and output of water, though it is unusual for there to be any important disturbance of electrolyte balance. If a wound infection develops, the dose of cortisone should be increased.

Hypotension.—In the days immediately after operation a few patients have experienced an orthostatic hypotension; such patients may be fairly comfortable when lying in bed, but the pulse is soft, and even the sitting posture may cause a feeling of exhaustion. Increased dosage of cortisone has been recommended for such patients, but in one such case the hypotension did not pass off for seven days in spite of a temporarily increased daily dose of 100 mg. of cortisone. Sudden crises of hypotension occasionally occur in the first few weeks or months after operation and may call for the administration of increased cortisone or intravenous hydrocortisone. A persistent postural hypotension can usually be corrected by the administration of DOCA in doses of 5 mg. daily, while if the phase of hypotension is very prolonged the longer-acting deoxycortone trimethyl acetate in doses of 30–50 mg. by intramuscular injection once every six or eight weeks can be used (Thorn and Jenkins, 1952). In patients who do not feel completely fit after adrenalectomy postural hypotension should always be looked for and corrected. The use of DOCA in hypertensive cases is not without danger.

Salt Withdrawal.—In 1 case in the series in which, owing to a misunderstanding of instructions ten days after operation, there had been a low daily intake of salt for a week or more, the patient became enfeebled and mentally depressed, lost her appetite, and experienced a return of the pre-operative pain; the pulse became rapid and soft and she had a postural hypotension. The serum sodium and chloride were low. Clinical improvement occurred slowly following the administration of sodium chloride and hydrocortisone intravenously and an increased daily dose of cortisone intramuscularly.

Emergency Symptoms.—In 3 cases nausea followed by vomiting, possibly brought on by a chill, resulted in the patient becoming ill with weakness and hypotension many weeks after operation. Vomiting is one of the first symptoms of acute adrenal insufficiency and when continued it may ensure the loss of orally ingested cortisone following which the patient's condition deteriorates rapidly. One such patient was relieved in forty-eight hours by the intramuscular injection of 200 mg. cortisone daily. In another patient in whom vomiting had gone on intermittently for a fortnight, initiated by an upper respiratory infection, there was great prostration, weakness, and hypotension and a return of pain in the bones; she had contrived to take her cortisone daily in spite of her nausea, and sufficient must have been absorbed for her to maintain a precarious hold on life. By the time she was re-admitted to hospital, Addisonian pigmentation had developed. A rapid improvement followed the intravenous injection of 100 mg. of hydrocortisone with intramuscular injections of cortisone in doses of 50 mg. eight-hourly.

In some patients in whom there has been no regression of cancer after operation and who therefore are slowly dying of their disease (and especially those with abdominal symptoms), the clinical diagnosis of cortisone deficiency may not be easy. Hart (1955) records 3 cases of delayed post-adrenal crises in which intravenous hydrocortisone was effective. It is important that both patient and practitioner understand the need for the parenteral administration of cortisone in such emergencies.

Any collateral disease, such as an acute bronchitis or pneumonia, a septic wound, a major illness, and especially a surgical operation (including even a dental extraction), requires the administration of an increased dose of cortisone during and after the period of the illness, and this fact should be brought to the notice of the patient and her doctor before discharge from hospital.

RESULTS

The results are shown in the following table:—

Cases improved:—		
Major remission, patients alive and well	9	
Major remission, patients alive but now relapsing	5	
Major remission, followed by relapse and death	7	
Major remission, followed by death from other causes	3	
	—	24
Cases unimproved:—		
Died of cancer without clinical improvement	14	
Alive but not showing improvement	4	
Post-operative deaths	6	
	—	24
Too early for assessment:—		
Alive and well	5	
	—	5
Total		53

Of the 53 cases operated on, there have been 6 post-operative deaths, all in advanced cases. Two patients died only a few hours after operation and I have referred to these earlier in this paper; the others died from cancer or from cardiac failure. Twenty-four cases have achieved an objective remission; 9 of these are alive and well after periods of up to two years and four months. The patient with the lowest remission (2 years, 4 months) who was one of the worst cases in the series (*Case* 2) is still free from all clinical and radiographic signs of cancer. Fourteen cases have died of cancer without clinical improvement, 4 are alive but have not shown improvement, and in 5 cases it is too early for an assessment of progress to be made.

Fig. 81 shows the duration in months of the remission and of the subsequent relapse in 24 cases. The response in the most successful cases is dramatic, the patient experiencing a return to normal health. In some cases the response is short, being only of a few months' duration; but in 3 cases in the series there have been regressions of two years or more, 2 of them being still free from recurrence while in 1 the cancer has become reactivated.

Regression has been most common in skeletal and pulmonary metastases. Allowing for the fact that the breast had been previously removed in most of the cases treated, the proportion of the cases in which regression occurred in the primary growth, or a metastasis in the opposite breast, was high. Skin nodules have disappeared and metastases in the central nervous system and in the liver have resolved in a few cases. (*Table II.*)

When the cutaneous nodules disappear, a subsequent reactivation of growth in the skin does not manifest itself at the site of the original nodule but

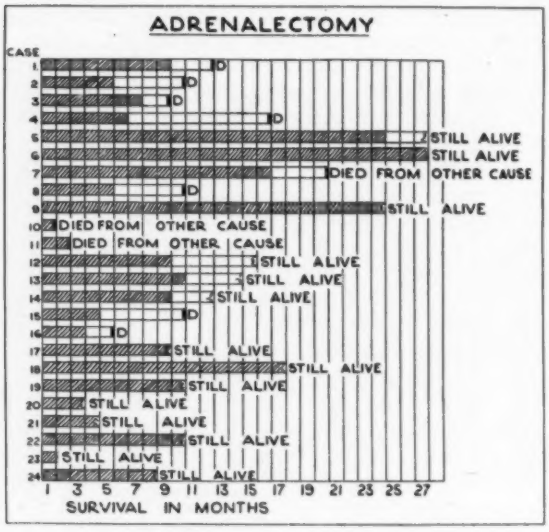


FIG. 81.—Duration of remission in 24 cases.

elsewhere. When skeletal metastases resolve, the bone may return almost to its normal density and structure, whereas in other cases there are sclerosed areas enclosing osteoporotic foci which suggest that cancer cells may be still present but are walled off by dense bone. It has not been practical to do a bone biopsy in these cases.

The following case reports give the clinical details of some of the successful cases.

Table II.—FREQUENCY OF REGRESSION IN DIFFERENT SITES IN 24 CASES

	Cases
Primary breast	6
Cutaneous nodules	5
Lungs	8
Bones	16
Central nervous system	4
Liver	2

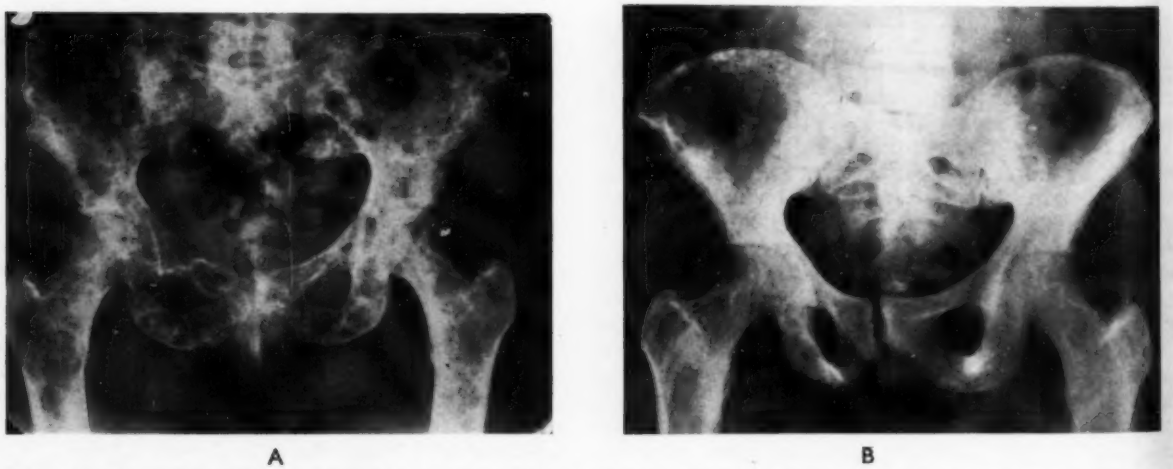
CASE REPORTS

Case 2.—A woman (V. D.), aged 36 years, had a right radical mastectomy for spheroidal-celled carcinoma of the breast in March, 1948. In Jan., 1952, she began to have pains in the spine and pelvis, which were shown on radiography to be the seat of metastases. She received treatment by stilbœstrol and testosterone, which gave partial symptomatic relief.

ON EXAMINATION (Aug. 1, 1953).—The patient had been bedridden for eight weeks and movement of the limbs in bed was restricted because of pain. She complained of pain in the right hip, right leg, and dorsal and lumbar spine. She had lost her appetite and also a considerable amount of weight. The right arm was swollen. She had a large ulcerated sacral bedsore. Radiography revealed very extensive osteolytic deposits in the entire thoracic and dorsal spine and the pelvis (*Fig.* 82 A), both femora (*Fig.* 83 A), and both tibiæ.

OPERATION.—Bilateral adrenalectomy and oöphorectomy (one-stage) were carried out on Aug. 7. The ovaries were the seat of malignant disease.

RESULT.—Pain was relieved in the first few days. The improvement at first was slow. It was evident in four weeks after operation that recalcification of the bones was taking place. She was not moved out of bed until one month after operation because of the danger of a fracture of one of the osteoporotic bones. The bedsore slowly healed. The swelling of the right arm disappeared. In the next two months rapid recalcification of the vertebræ, the pelvis, and bones of the legs occurred. She regained normal activity and was able to do some housework four months after operation. When seen two weeks ago she was in good general health, able to look after her family, and do the family washing. There are now no clinical and no radiographic signs of active disease or of recurrence. The period of regression is two years, four months. This case is the most striking in the series because the cancer was so extensive and because of the long period of survival. *Fig.* 82 B shows a radiograph of the pelvis in November, 1955. *Fig.* 83 B shows the right femur before and two months after adrenalectomy; both femora and tibiæ presented a similar appearance before operation.



A B

FIG. 82.—*Case* 2. A, Massive malignant invasion of all the bones of the pelvis and upper parts of both femora before operation (Jan. 31, 1952). B, Radiographs showing recalcification of the same bones 27 months later (Nov. 1955).

Case 3.—A man (H. K.), aged 50 years, first noticed a mass in the right breast in 1951. He had no treatment until he attended hospital in January, 1953, when some radiotherapy was given. A biopsy of the growth showed a mixed spheroidal-celled carcinoma and adenocarcinoma.

ON EXAMINATION (July 1, 1953).—There was an ulcerating cancer of the right breast fixed to the chest

wall, the diameter of the ulcerated part being 6 cm.; scattered over the upper part of the trunk, on the sides and the back of the neck, and on both arms were about a hundred skin metastases, some small and shotty, others up to 1 in. in diameter (*Fig.* 84 A). Radiography showed extensive secondary deposits in both lungs (*Fig.* 85 A).

OPERATION.—Bilateral adrenalectomy and orchidectomy (one-stage) were done on July 11. Metastases were present in both adrenal glands.

RESULT.—The growth of the right breast disappeared completely and healed by firm, though telangiectatic skin (*Fig.* 86). Most of the skin nodules disappeared except a few of the largest ones, which were reduced to about one-third of their original size (*Fig.* 84 B). The pulmonary deposits became radiotranslucent (*Fig.* 85 B). The patient's general health greatly improved. *Fig.* 87 shows the spheroidal-celled structure of one of the skin nodules and *Fig.* 88 shows the fibrous remains of another nodule with some persisting degenerate cancer cells several weeks after adrenalectomy. In July, 1955, after a remission of two years, he noticed that a few new skin nodules were appearing in the abdomen and arms. Radiography in September, 1955, showed osteolytic metastases in the pelvic bones and in the left scapula. The patient is still alive and mobile, though his condition is slowly deteriorating. In this case, although he has had a long remission and has felt fit and well, he has never been completely free from cancer, although it has been clinically at a standstill. The evidence for this has been the three or four skin nodules which have persisted on the trunk and neck, much reduced in size from what they were before operation.

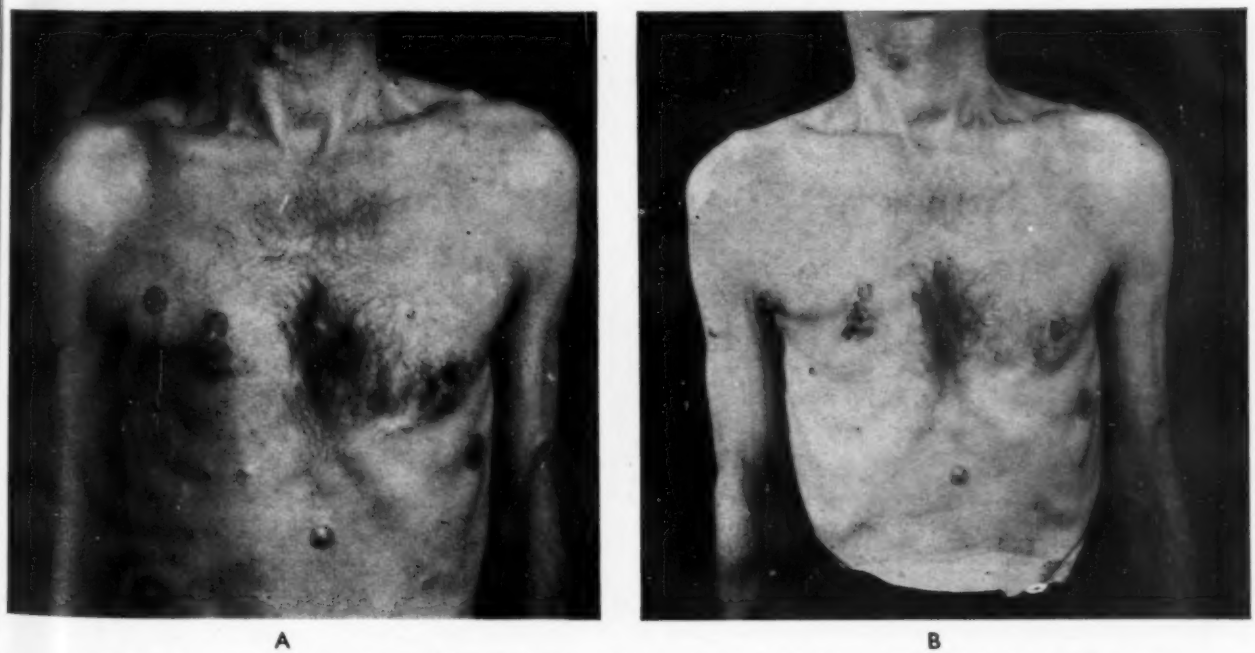
Case 4.—A woman (M. B.), aged 45 years, had a simple amputation of the left breast in April, 1950, for duct carcinoma. In October, 1952, she had a recurrence on the same side, which was treated by removal of the recurrent mass together with the underlying pectoral muscles and the axillary lymph-glands. Later she developed further diffuse recurrence in the skin, which was treated by radiotherapy and testosterone. The condition improved considerably and later relapsed.

ON EXAMINATION (Oct. 5, 1953).—She had several skin metastases in the operation area and some of those over the mastectomy scar were ulcerated. There was diffuse carcinoma in the right breast. Radiography revealed no osseous metastases and the chest was clear.

OPERATION.—Bilateral adrenalectomy and oöphorectomy (one-stage) were completed on Oct. 21.

A B

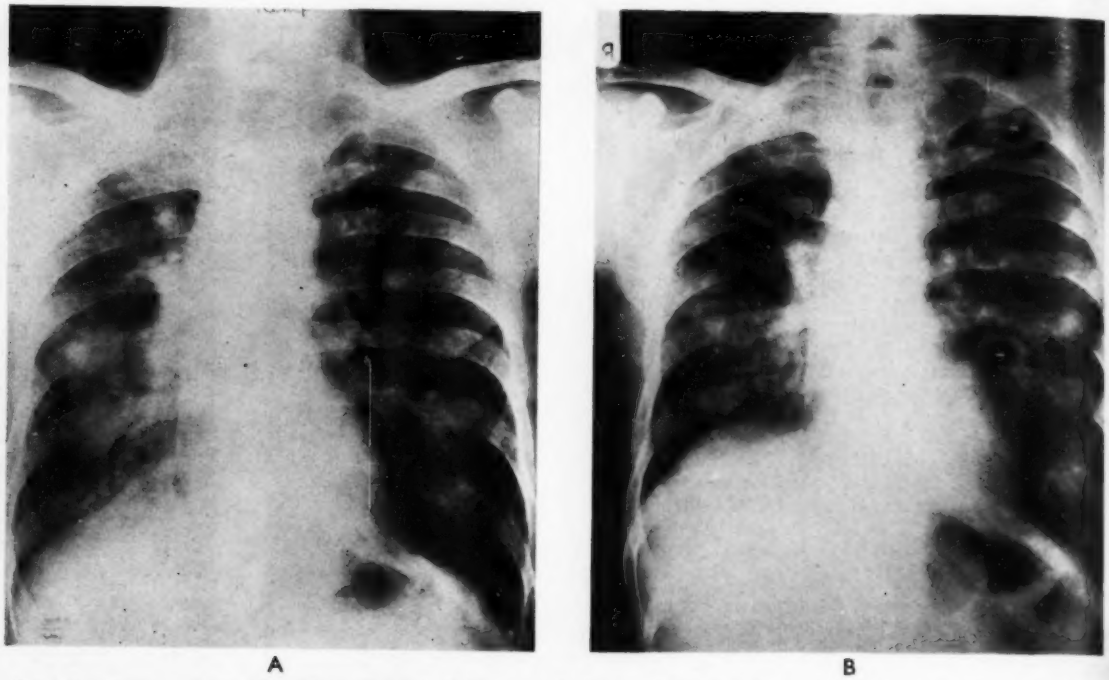
FIG. 83.—*Case* 2. A, Pre-operative radiograph of extensive invasion of the left femur with metastatic cancer (Aug. 1, 1953); B, Radiograph showing recalcification nine weeks after adrenalectomy and oöphorectomy (Oct. 14, 1953).



A B

FIG. 84.—*Case* 3. A, Pre-operative condition showing inoperable carcinoma of right breast with multiple skin nodules over trunk, neck, and arms. B, Post-operative condition. The breast is healed, nearly all the skin nodules have disappeared except a very few of the largest ones, which are reduced in size.

RESULT.—The nodules in and around the mastectomy operation scar disappeared, the right breast became much softer and of almost normal consistency. Radiography of the chest and bones remained negative. The patient's well-being returned and she was able to carry on with her normal housework. Sixteen months after operation a few small nodules appeared on the left chest wall and biopsy showed them to be infiltrated by carcinoma. In other respects she was still well. She was admitted to hospital as an abdominal emergency on July 6, 1955, suffering from shock, generalized abdominal pain, and fæculent vomiting, and was believed to have generalized abdominal metastases with intestinal obstruction. She died on July 7 without any operation having been performed. Autopsy showed no evidence of cancer in the lungs, mediastinum, alimentary tract, or in any of the bones which were examined. The cause of death was a volvulus of the small intestine for which no cause was found. The liver contained a few small nodules of secondary growth, none being larger than 1 cm. in diameter. Examination of the right breast showed no evidence of carcinoma. This patient died of intestinal obstruction, which was mistaken for abdominal malignant disease, and death was probably accelerated by a cortisone deficiency consequent upon the vomiting. She had a remission of almost twenty-one months, and although a few very small foci of cancer in the skin and in the liver were found, the rest of the body was free from cancer.



A B

FIG. 85.—*Case* 3. A, Pre-operative radiograph (July 7, 1953) showing bilateral pulmonary metastases; B, Post-operative radiograph (Sept. 10, 1953) 2 months after operation. Great improvement in pulmonary metastases.

FIG. 86.—*Case* 3. Close-up view of the area including the breast previously occupied by growth. The skin is composed of sound epithelium with much telangiectatic change.

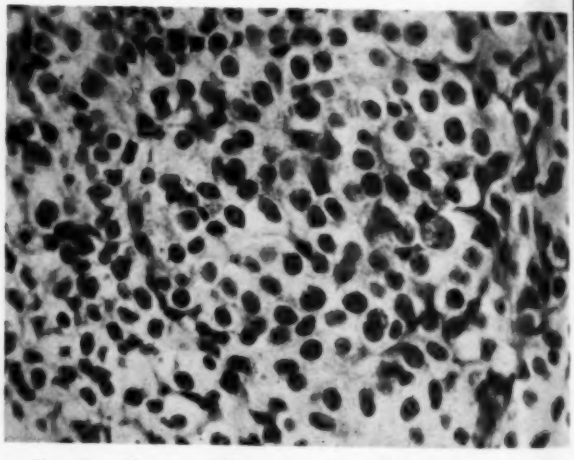


FIG. 87.—*Case* 3. Microscopy of a skin nodule showing spheroidal-cell carcinoma. (× 325.)

Case 5.—A woman (A. B.), aged 46 years, had a right radical mastectomy for a mixed adenocarcinoma and cellular carcinoma simplex in October, 1951. In the autumn of 1953 she developed pain in the left hip and a bad limp. She had lost weight and felt ill.

ON EXAMINATION (June 10, 1954).—The operation area was normal and there was no local recurrence.

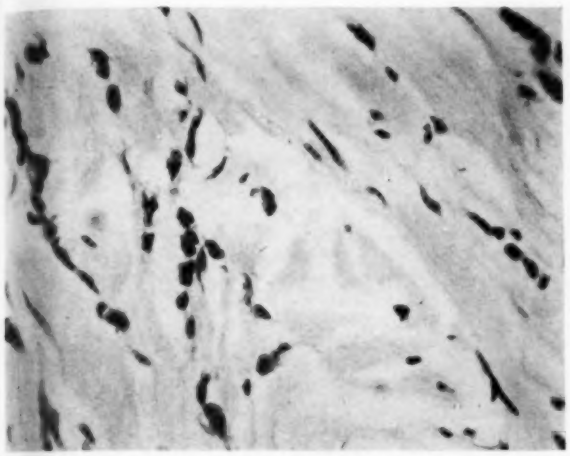
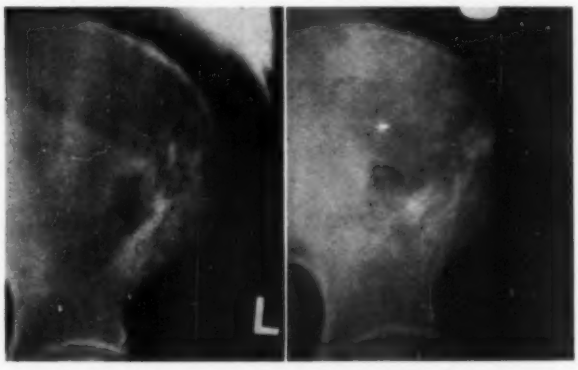


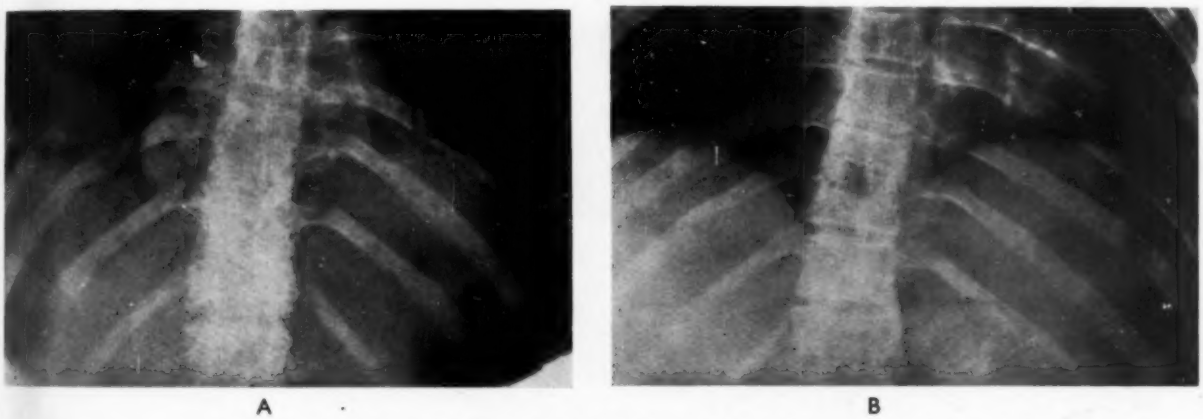
FIG. 88.—*Case* 3. Microscopy of skin previously occupied by a skin nodule. There are some degenerate-looking cancer cells in the midst of fibrous tissue. (× 325.)

1952, for carcinoma. In June, 1952, she began to have pain in the back, the right side of the abdomen, and the right thigh. Radiography in March, 1953, showed metastases in the ribs and the lower lumbar vertebræ, with collapse of the fourth and fifth lumbar bodies. Radiotherapy was given to the lumbar spine and testosterone was given by injection. With the aid of a spinal support she was able to get about until September, 1953, when, following severe pain in the back, she became unable to walk.



A B

FIG. 89.—*Case* 5. A, Pre-operative radiograph showing metastasis in left ilium (June 10, 1954); B, Post-operative radiograph showing clinical improvement with moderate degree of bony sclerosis five months later (Oct. 20, 1954).



A B

FIG. 90.—*Case* 6. A, Pre-operative radiograph (Nov. 1, 1953) showing multiple translucent secondaries in all the lowest ribs; B, Post-operative radiograph (Aug. 1, 1954) showing recalcification with disappearance of most of the translucent areas.

There was a large mass in the left lobe of the liver believed to be a metastasis. Radiography showed massive secondary deposits in the anterior part of the left iliac bone (*Fig.* 89 A).

OPERATION.—Bilateral adrenalectomy and oöphorectomy (two-stage) were completed on June 22, 1954.

RESULT.—The pain in the hip was greatly reduced and gradually disappeared. The patient felt well and gained weight. The mass in the abdomen diminished in size. Radiography showed sclerosis in the metastasis in the ilium (*Fig.* 89 B). After twelve months the pain and the limp in the left leg returned. Examination on Nov. 5, 1955, showed osteolysis and relapse of the metastasis in the ilium, a new swelling in the right lobe of the liver, and a cutaneous nodule on the right shoulder. She had had a remission of twelve months and is still alive seventeen months after operation.

Case 6.—A woman (D. R.), aged 33 years, had a left simple mastectomy followed by radiotherapy in January,

ON EXAMINATION (Nov. 1, 1953).—The patient was ill, with a raised pulse-rate and evidence of loss of weight. There was tenderness in the dorsal and lumbar spine and over various ribs. She was unable to get out of bed. Radiography showed collapse of the tenth and twelfth dorsal vertebræ in addition to collapse of the fourth and fifth lumbar bodies from deposits of cancer, with widespread metastases in the ribs (*Fig.* 90 A) and pelvis (*Fig.* 91 A).

OPERATION.—Bilateral adrenalectomy and oöphorectomy (two-stage) were completed on Nov. 24, 1953.

RESULT.—There was rapid relief of pain, an increasing sense of well-being, and gradual recalcification of the bones. *Fig.* 91 B shows the pelvis nine months after operation. The vertebræ consolidated though retaining their wedge-shaped diameter. Small osteolytic metastases in the lower ribs completely resolved (*Fig.* 90 B). When seen ten months later she was able to do her housework and had put on weight. When seen one month ago,

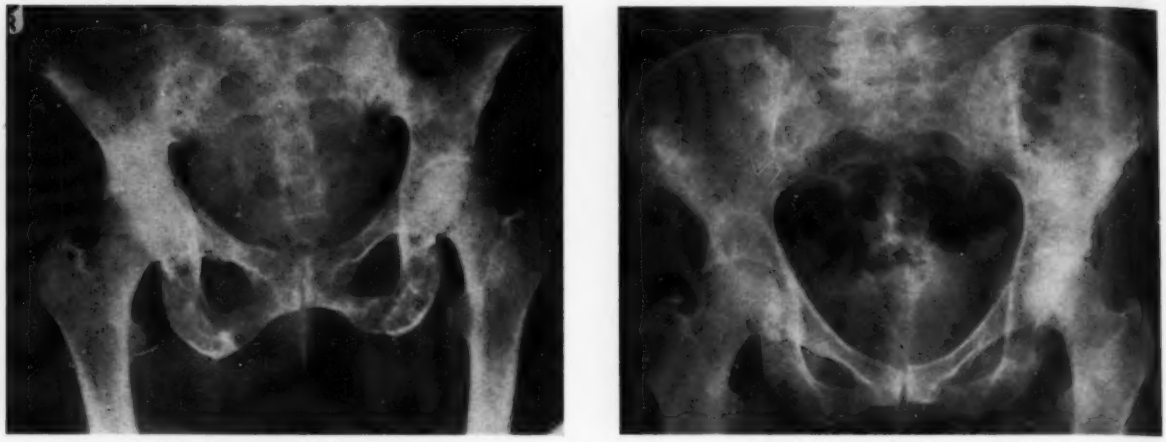
almost two years since her operation, her general condition was very good. She has had a remission of two years.

Case 7.—A woman (F. H.), aged 36 years, had a radical amputation of the left breast for intraduct carcinoma in December, 1946. In January, 1954, she developed a recurrent malignant skin nodule, attached to the chest wall at the inner end of the operation scar, which was treated by radiotherapy. In September, 1954, she developed aches and pains in the chest, the left shoulder, and the legs.

ON EXAMINATION (Jan. 15, 1955).—Small skin nodules in the chest wall could still be felt. Radiography showed osseous metastases in many ribs, the left scapula (*Fig.* 92 A) and the left ilium (*Fig.* 93 A), with probable early metastases in the sternum, left clavicle, and several vertebræ.

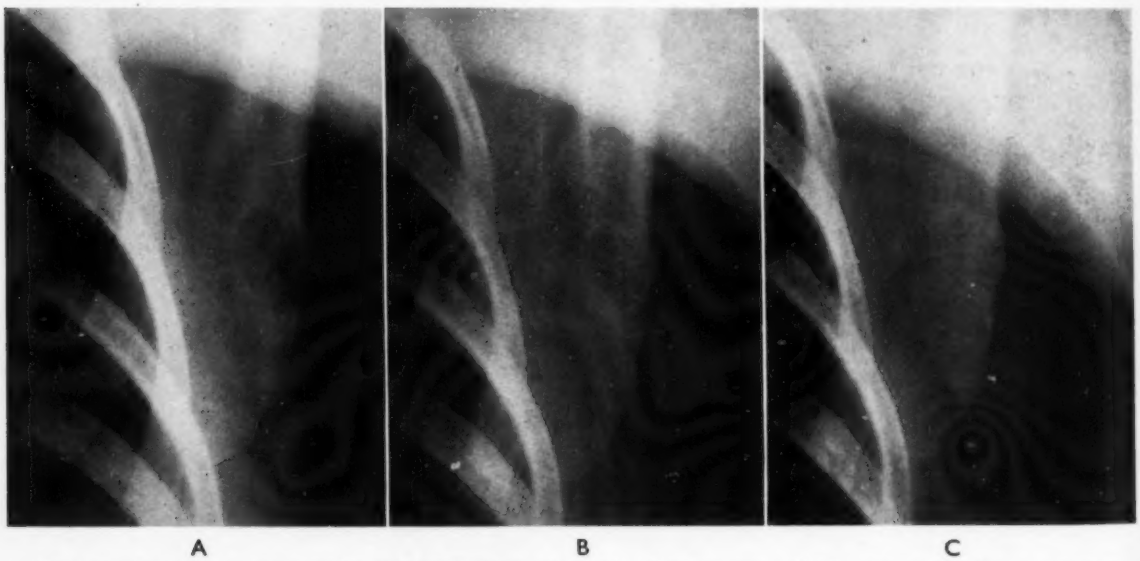
OPERATION.—Bilateral adrenalectomy and oöphorectomy (one-stage) were done on Feb. 4, 1955.

RESULT.—She made a satisfactory recovery and rapidly regained her sense of well-being. There was prompt relief of pain. The blood-pressure tended to be a little low for a time. Radiography on Oct. 18, 1955, showed recalcification of ribs, vertebræ, and left scapula. The original osteolytic metastasis of the scapula became walled round by dense sclerosed bone and gradually the cavity reduced in size and disappeared (*Fig.* 92 B, C). Similar



A B

FIG. 91.—*Case* 6. A, Pre-operative radiograph (Nov. 1, 1953) of pelvic bones and upper end of femora showing extensive metastatic carcinoma. B, Post-operative radiograph (Sept. 26, 1954) of the same bones showing extensive recalcification.



A B C

FIG. 92.—*Case* 7. A, Pre-operative radiograph (Jan. 18, 1955) of lower part of left scapula showing a metastasis. B, Post-operative radiograph four months after operation showing considerable sclerosis of the metastasis. C, Post-operative radiograph (Oct. 18, 1955) seven and a half months after operation, showing that the translucent metastasis has been filled in by sclerosed bone.

(though not so complete) sclerosis occurred in a metastasis of the ilium (*Fig.* 93 B, C). The patient is doing her housework and is in good general health and free from pain ten months after operation.

Case 8.—A woman (D. H.), aged 45 years, had a left radical mastectomy followed by post-operative irradiation for spheroidal-celled carcinoma in May, 1954. In February, 1955, she complained of drooping of the left eyelid, pain above the left eye, and pain in the left chest.

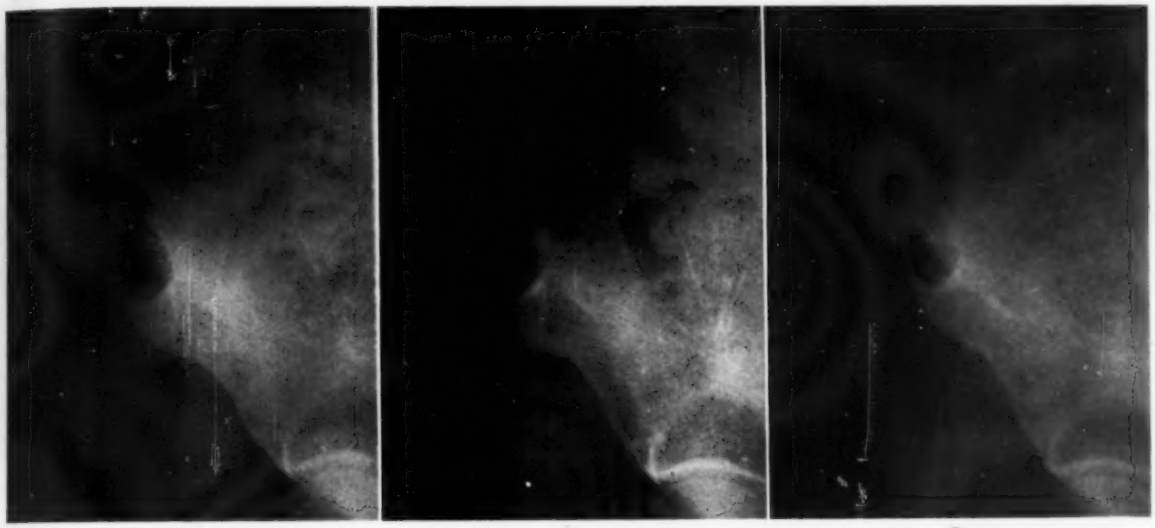
ON EXAMINATION (March 1, 1955).—There was marked ptosis of the left eyelid, with enophthalmos (*Fig.*

94 A). Radiography showed a fracture of the right sixth rib (*Fig.* 95 A); there was a shift of the mediastinum to the left and in the lateral film of the chest there was an opacity in the left hilum region; there was a possible metastasis in the left side of the vault of the skull.

OPERATION.—Bilateral adrenalectomy and oöphorectomy (one-stage) were done on March 16, 1955.

The next two cases are recorded because they are examples of metastases in the central nervous system which have responded to bilateral adrenalectomy and oöphorectomy.

Case 9.—A woman (D. G.), aged 50 years, had radical mastectomy of the right breast in April, 1953.



A B C

FIG. 93.—*Case* 7. A, Pre-operative radiograph (Jan. 21, 1955) showing rounded translucency in the left ilium, due to a metastasis. B, C, Post-operative radiographs (June 1 and Oct. 18, 1955) showing gradual sclerosis of the metastasis, four months and seven and a half months after adrenalectomy. In the last radiograph there is still part of a cavity.

A B

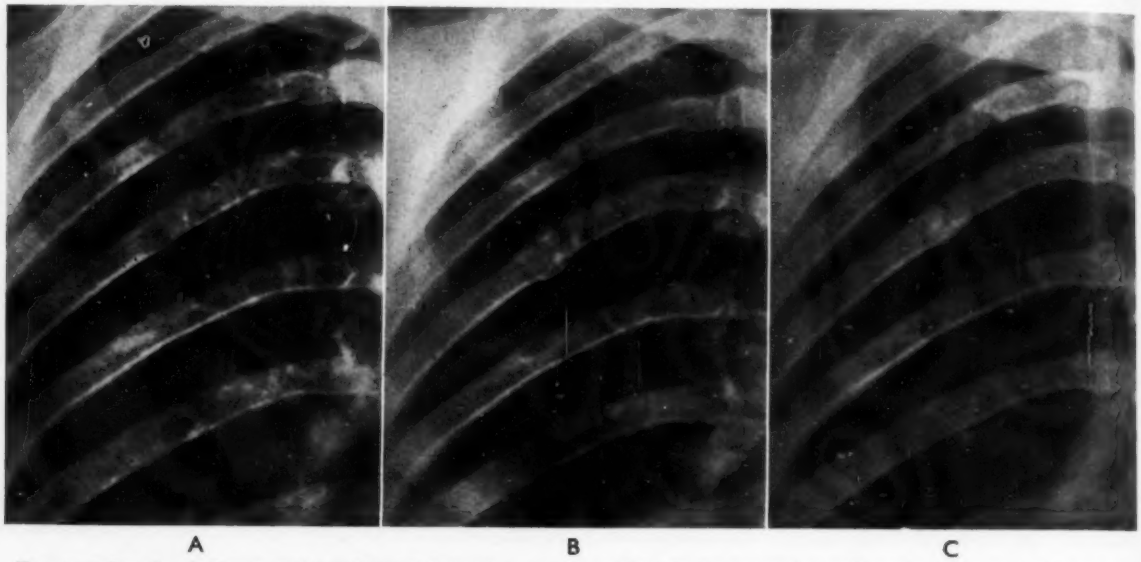
FIG. 94.—*Case* 8. A, Pre-operative photograph of the face showing enophthalmos and pseudoptosis of the left eye. B, Post-operative photograph (May 5, 1955) seven weeks after operation, showing the return of the left eye to normal.

RESULT.—When seen on May 5, the eye and the eyelid had returned to normal (*Fig.* 94 B). Radiography of the chest showed a healing fracture of the right sixth rib (*Fig.* 95 B, C) with disappearance of the mediastinal shadow. When seen on Nov. 1 she was doing full work and was entirely symptom-free and able to play golf.

Microscopically the growth was adenocarcinomatous, having both a trabecular and an acinar pattern. In February, 1955, she developed weakness of the muscles of the left leg, which grew steadily worse, so that she had great difficulty in getting about. The operation area remained normal.

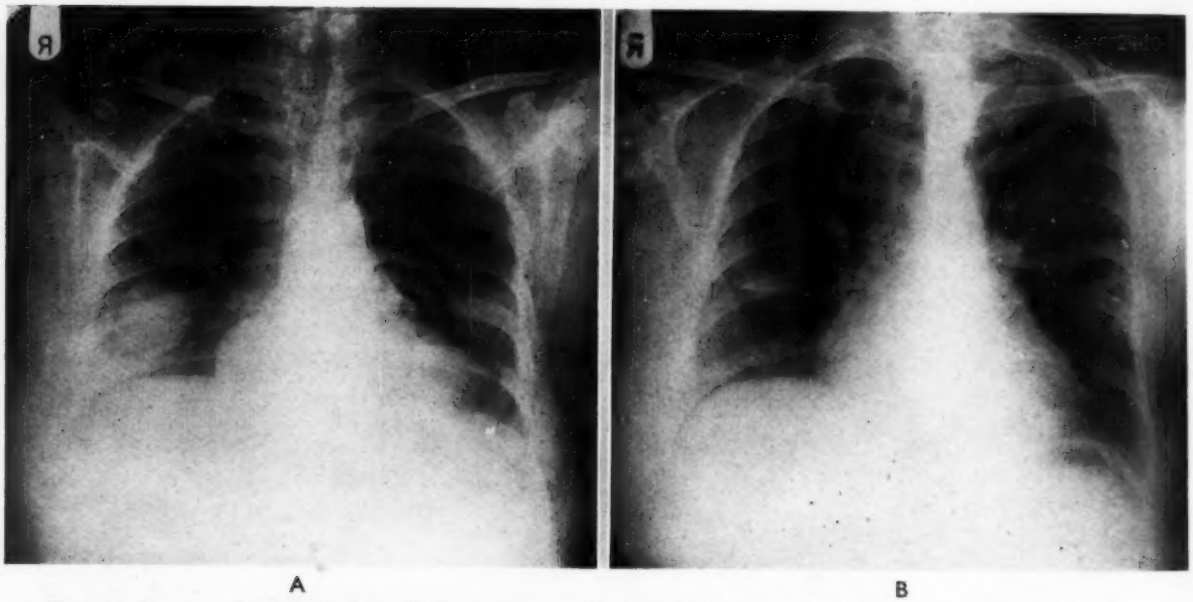
ON EXAMINATION (March 15, 1955). (In consultation with Dr. H. G. Garland).—There was generalized weakness of the muscles of the left leg with some increase of tone; both plantar reflexes were sharply extensor, and there was no sensory loss. A diagnosis was made of early spinal compression from secondary carcinoma.

Case 10.—A woman (M. B.), aged 59, had a left radical mastectomy for carcinoma in 1941. She remained well until early in 1955, when she suddenly lost, almost completely, the sight of the left eye. In April, 1955, she began to experience loss of memory and progressive and severe dysphasia; there was loss of weight and much



A B C

FIG. 95.—*Case* 8. A, Pre-operative radiograph (March 1, 1955); and B, C, Post-operative radiographs (May 10 and Nov. 3, 1955) showing a fine linear fracture of the rib through a metastasis, with sound healing by callus formation.



A B

FIG. 96.—*Case* 10. A, Pre-operative radiograph (July 5, 1955) showing biggish rounded metastasis lower pole of each lung. B, Post-operative radiograph (Oct. 24, 1955), twelve weeks after operation, showing disappearance of pulmonary metastases.

OPERATION.—Bilateral adrenalectomy and oöphorectomy (one-stage) on April 5, 1955; both adrenals and both ovaries were the seat of cancer.

RESULT.—The pain was relieved very soon after operation and the muscular weakness started to improve and later she was able to walk about. When seen on Nov. 30, she had been able to walk about for the past several months and all muscular weakness in the left leg had disappeared. In the last few weeks she has complained of a little pain in the left foot for which she is under investigation. She has had a remission of eight months.

enfeeblement. She was admitted to hospital under the care of Dr. H. G. Garland, whose investigations pointed to the existence of secondary deposits of cancer in the brain.

ON EXAMINATION (July 5, 1955).—The scar of the left radical mastectomy was normal, the right breast was normal, and there were no palpable glands. The patient was mentally affected and her power of co-operation was markedly impaired. She could only write with difficulty and very badly; she was quite unable to fill in the numbers on a clock face and she could not make any attempt

at drawing a house. There was a good deal of apraxia and a left partial hemiplegia with marked loss of power of the muscles of the left arm and leg. She had jactitatory movements of both arms. Radiography showed a large, round metastasis in each lung (*Fig.* 96 A).

OPERATION.—Both ovaries were removed on July 15, 1955, the patient being considered unfit for primary adrenalectomy. In two weeks the patient showed a dramatic improvement; her memory returned and with it her power of co-operation; she could converse normally. The mental changes disappeared as did the jactitatory movements of the arms which had been present before operation. By Aug. 2 (seventeen days after the first operation), so great had been the improvement in her condition that bilateral adrenalectomy (one-stage) was carried out.

RESULT.—Further considerable improvement followed. When seen on Nov. 20 the patient spoke rationally, was mentally normal and alert, and her memory appeared to be normal. The muscular power of the left arm and leg were normal and she walked normally. She had put on a little weight and her general appearance and bearing were dramatically improved, being those of a normal woman. Radiography showed complete disappearance of the pulmonary metastases (*Fig.* 96 B).

HYPOPHYSECTOMY FOR METASTATIC MAMMARY CANCER

Suppression of the gonadotrophic hormones by removal of the pituitary gland may bring about a complete cessation of œstrogenic activity. Hypophysectomy has therefore been recently considered as a primary procedure for the relief of metastatic mammary cancer. Similarly in those cases in which removal of the adrenals and the ovaries have been followed first by a remission and later by a relapse, subsequent removal of the pituitary may, by removing the stimulus to œstrogen production in any hypertrophied adrenal rests, bring about a further remission.

Removal of the pituitary should also abolish the source of *growth hormone* which, according to some workers, may promote the growth of malignant tumours just as it promotes growth in normal tissues. There is evidence for this in an observation of Pearson, West, Hollander, and Treves (1954), who reported a patient with metastatic mammary cancer in whom the disease recurred after castration and adrenalectomy, and who later had a remission following hypophysectomy. In the third month after hypophysectomy growth hormone was given to the patient in order to determine if tumour growth could be stimulated; during the period of administration the amount of urinary calcium excreted daily (which they believe to be a guide to the amount of bone destruction resulting from active tumour growth), was found to be significantly increased as against that in the control period; they believed that this finding supported the view that growth hormone may be a stimulus to tumour growth.

In the experimental animal it has been shown by Martinez and Bittner (1954) that in miee having spontaneous mammary tumours hypophysectomy resulted in a regression of the tumours in 11·5 per cent of the animals, while bilateral adrenalectomy alone, or combined with oöphorectomy, produced a regression in 3·3 per cent and 3·7 per cent of the animals respectively. Mühlbock (1953) has further shown that frequent implantations of fresh hypophyses into mice induce mammary neoplasia in the absence of extraneous œstrogen and of the milk factor; this finding suggests that a pituitary hormone plays a part in the development of the disease.

For the treatment of mammary cancer with metastases, hypophysectomy and also treatment of the pituitary gland by irradiation has been done in a few cases with some regressions.

Hypophysectomy: Perrault (1952) reported the first case of hypophysectomy for a patient with metastatic mammary cancer; the patient had pulmonary metastases and some improvement followed the operation.

Luft, Olivecrona, Sjogren, Ikkos, and Ljunggren (1955) reported 37 cases of metastatic mammary cancer treated by hypophysectomy. In 4 of the early cases the hypophysis was incompletely removed, and 3 patients died soon after operation from various causes. Of the 30 remaining cases 16 are dead and 14 alive from six months to two and a half years after hypophysectomy. All the cases with cerebral and/or hepatic metastases have died, except one. If these cases are excluded, there remain 23 cases, of which 13 are alive and 10 are dead.

Driesen (1955) reported 6 cases of advanced mammary cancer treated by hypophysectomy. One patient died shortly after operation, in 2 others there was no response, and in 1 case extensive metastases within the skull made it impossible for the surgeon to reach the hypophysis. In a further case, a woman of 48, who had a pathological fracture of a lumbar vertebra, operation was followed by relief of pain and healing of the fracture. In another case, a woman aged 40, with widespread skeletal metastases and a local recurrence in the scar of the breast operation and in the axillary gland, there was considerable subjective and objective improvement after three and a half months, with the disappearance of the recurrence in the operation scar and recalcification of skeletal metastases. In 2 of the fatal cases autopsy showed that portions of the pituitary gland had been left behind.

Pituitary Irradiation has been used in an effort to destroy pituitary hormones. Douglas (1952) reported irradiation of the pituitary, but in only 2 of 37 patients was there any response. One of these was a postmenopausal patient who had a recurrent malignant mass over the sternum. The second was a woman of 46 who had benefited from ovarian irradiation but who later had relapsed; she had a regression of ten months. The treatment was not well tolerated.

Radon Seeds to the Pituitary: Instead of removing the pituitary gland, Forrest and Brown (1955) have irradiated it by introducing radon seeds through a cannula into the pituitary fossa by way of the nose and the sphenoidal sinus, using radiographic control. Nine cases of advanced cancer have been treated by this method without mortality or morbidity, the only complaint being of a mild headache on the evening of the operation. No report of the late results is yet available.

CARCINOMA OF THE PROSTATE

Huggins and Clark (1940) showed that spontaneous enlargement of the prostate in senile dogs regressed following orchidectomy or after the administration of œstrogen. It occurred to Huggins

and his co-workers that in those malignant tumours of the prostate in man in which the tumour cells were highly differentiated and resembled prostatic epithelium, there might be a favourable response to anti-androgenic procedures. A readily available œstrogenic substance of great activity and one which could be given by mouth had been synthesized in 1938 by Dodds, Goldberg, Lawson, and Robinson. In 1941 Huggins and Hodges showed that in some cases of prostatic carcinoma with bone metastases removal of the principal source of androgen by orchidectomy, or, alternatively, the partial suppression of androgen by the administration of œstrogens (for example, stilbœstrol), resulted in some cases in a clinical remission of the growth and in disappearance of the osseous metastases. Conversely, if androgens were administered the tumour was reactivated. Although eminently successful for a time in many cases, the period of regression terminates, apparently because androgenic hormones are synthesized elsewhere, possibly in the adrenal cortex (*Fig.* 97). Since these discoveries surgeons everywhere have been able to confirm the beneficial effects of orchidectomy and/or stilbœstrol in a considerable proportion of cases of carcinoma of the prostate. The urinary symptoms are improved, though sometimes resection of the obstructing mass has to be done. Metastases may be resolved.

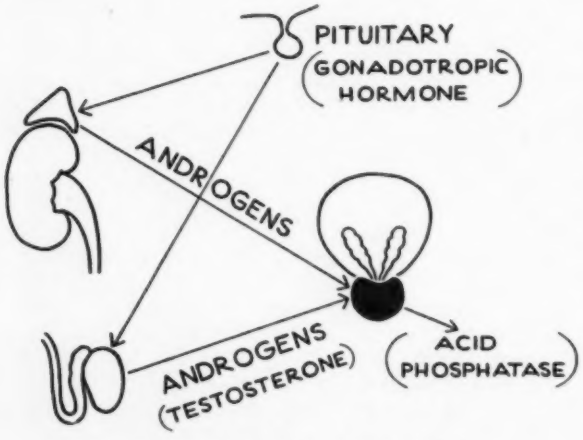


FIG. 97.—Hormonal relations of the prostate.

Some surgeons have preferred orchidectomy in the treatment of malignant prostate, others have preferred stilbœstrol alone, and many have used a combination. The following two case reports illustrate the improvement which may be obtained in prostatic cancer with metastases by treatment with orchidectomy combined with stilbœstrol and by treatment with stilbœstrol alone.

Case 11.—A man (W. M.), aged 72 years, complained of pain in the back and some urinary difficulty and frequency.

ON EXAMINATION (Feb. 10, 1954).—The prostate was hard and frankly malignant. Radiography showed widespread metastases in the pelvic bones (*Fig.* 98 A).

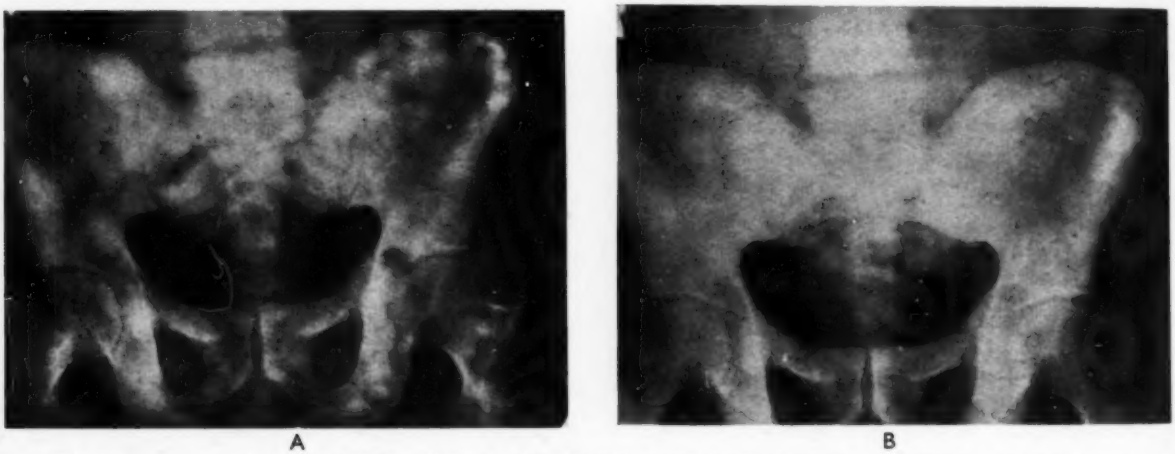
OPERATION.—Bilateral orchidectomy was carried out on Feb. 22. He also received treatment by stilbœstrol, 5 mg. three times a day.

RESULT.—The symptoms of bone pain completely disappeared and the urinary frequency and difficulty returned to normal. A radiograph (Aug. 17, 1955) shows that the pelvic bones have returned almost to their normal pattern (*Fig.* 98 B).

Case 12.—A man (J. K.), aged 58 years, had urinary symptoms of frequency and slight difficulty in micturition. He also had pain in the back.

ON EXAMINATION (Oct. 10, 1949).—He had a frankly malignant prostate which was infiltrating the periprostatic tissues. Radiographs showed a secondary metastasis, partly osteoporotic, partly osteosclerotic, in the left side of the pelvis, above the acetabulum (*Fig.* 99 A). He was given treatment by stilbœstrol 5 mg. three times a day.

RESULT.—Radiography on July 16, 1951, shows that the metastasis has now been replaced by normal bone (*Fig.* 99 B). The patient is entirely symptom-free.



A B

FIG. 98.—*Case* 11. A, Pre-operative radiograph showing widespread localized osseous metastases in pelvic bones; B, Radiograph after treatment by orchidectomy and stilbœstrol, showing very great improvement in the bone architecture.

A follow-up of the results of treatment of malignant prostate with and without metastases by *orchidectomy* and *stilbœstrol separately and together* was undertaken by a group of American surgeons and reported by Nesbit and Baum (1950). *Fig.* 100, taken from their series, shows that in cases with no metastases a *combination* of *orchidectomy* with *stilbœstrol* gave an appreciably better five-year survival rate than treatment by orchidectomy or stilbœstrol alone. The same applied in the case of malignant prostate with metastases.

In cases of malignant prostate which have become reactivated after initial control by anti-androgenic measures, Huggins suggested bilateral adrenalectomy with cortisone replacement. In my department 7 adrenalectomy for cancer of the prostate is much less successful than for cancer of the breast. In cases of malignant prostate treated by adrenalectomy it is not always easy to assess the extent or completeness of a

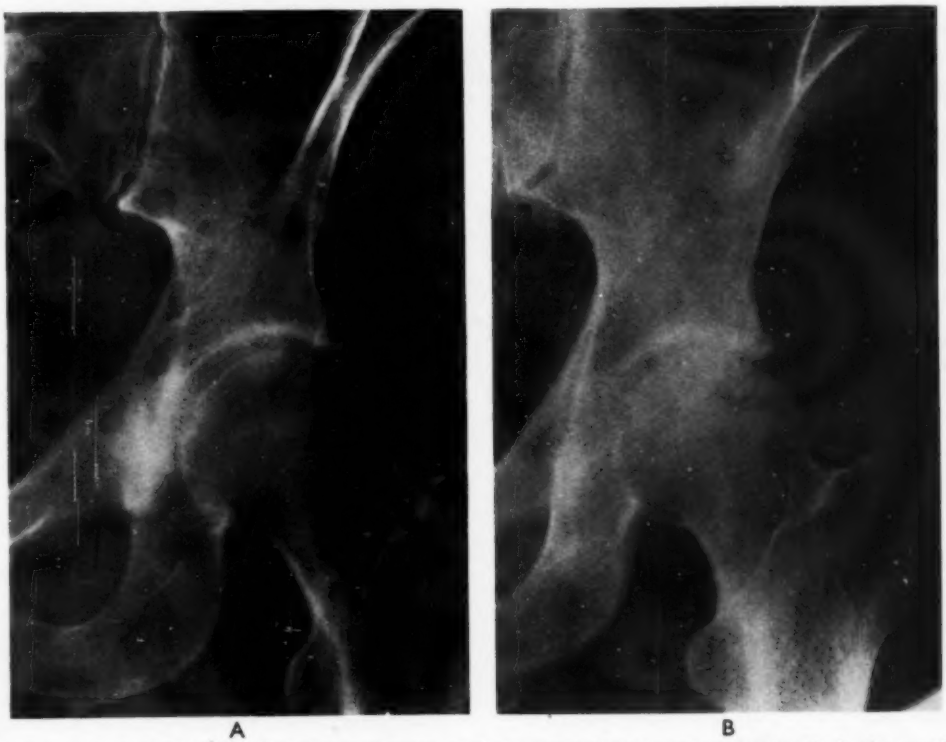


FIG. 99.—*Case* 12. A, Radiograph of osseous metastases, partly osteoporotic and partly osteosclerotic, in the superior ramus of the ischium above the acetabulum. B, Radiograph, twenty-one months after, showing return of the bone structure to normal following treatment by stilbœstrol alone.

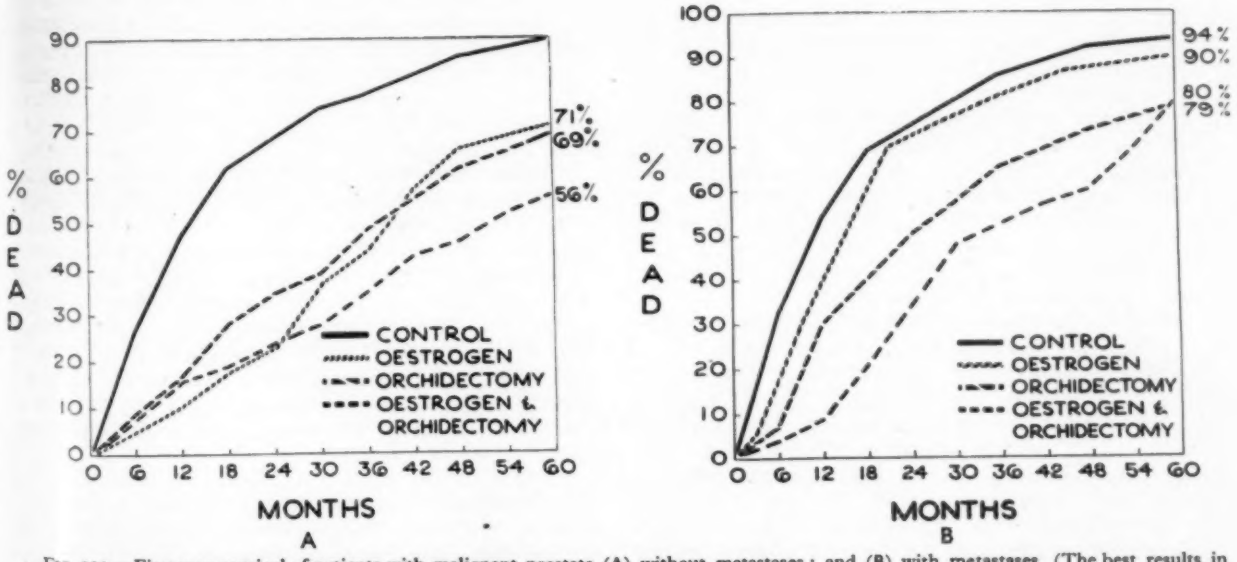


FIG. 100.—Five-year survival of patients with malignant prostate (A) without metastases; and (B) with metastases. (The best results in both series have been obtained by a combination of stilbœstrol and orchidectomy. This series is based on 1000 collected cases of malignant prostate by Nesbit and Baum (1950).)

cases have been dealt with in this way, but in only 1 case was there a short remission. Several, however, had relief of pain. Others have reported more favourably, but the consensus of opinion is that response. The radiographs of the osseous metastases do not always show the striking response seen in successfully treated cases of cancer of the breast, even when there appears to have been a clinical

response. It is not known why the results of adrenalectomy for metastatic prostatic cancer are inferior to those of metastatic mammary cancer when the rationale of the operation appears to be the same.

A few operations for the removal of the pituitary in cases of malignant prostate with metastases have been done by some surgeons, but it is too early to assess the results.

DISCUSSION

Reviewing our present knowledge of hormones in relation to cancer, we can say that certain cancers of the breast and of the prostate are *hormone-dependent*; in such cases, if the stimulating hormone

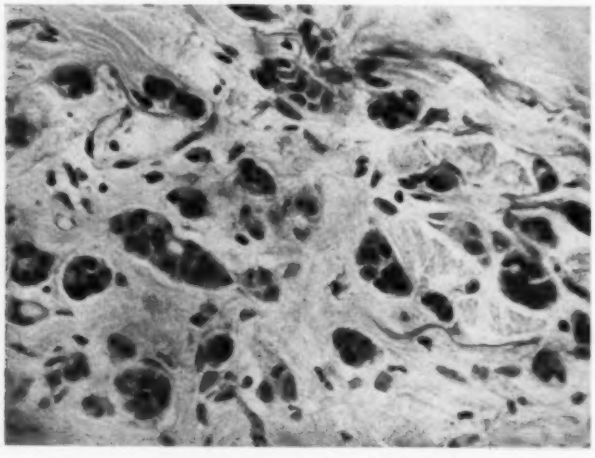


FIG. 101.—Photomicrograph showing alveolar type of carcinoma of the breast. Huggins advocated adrenalectomy, especially in cases having a micro-structure similar to this. The patient had a remission of eight months after operation. (× 325.)

is removed from the body by operation, or neutralized by giving an antagonistic hormone, the tumour regresses. Other tumours of these organs are *hormone-independent*. Possibly some tumours which first show a regression following removal of the hormonal stimulus but which later relapse, may have changed their character from a hormone-dependent tumour to a hormone-independent tumour, but we cannot be certain of this as yet; in some relapsing cases production of the stimulating hormone elsewhere in the body, as in glandular ' rests ', may bring about a reactivation of the tumour.

Mammary cancers may be classified into *œstrogen-dependent* and *non-œstrogen dependent tumours*. If the ovaries produce almost all the circulating œstrogen in the body in some premenopausal women and the adrenals either none at all or an amount below the threshold of tumour stimulation, then there may be a regression following oöphorectomy; the subsequent relapse may be due to a gradual increase in the output of œstrogen from the adrenal. In other premenopausal women a regression probably only follows the removal of both the ovaries and the adrenals. Within these limitations therefore we can use the terms *ovary-dependent* and *adrenal-dependent tumours*. In the postmenopausal group, when the ovaries are partly atrophied, the adrenals produce most of the œstrogen, hence the removal of the adrenals as well as the ovaries is necessary to bring about a regression. The evidence suggests that there is also a *growth-hormone dependent tumour*, so that hypophysectomy may cause a regression in some cases which have not been influenced by oöphorectomy and/or adrenalectomy.

Many prostatic cancers are *androgen-dependent* and *testis-dependent*; dependence upon the adrenal appears to be much less common than in mammary cancers.

The usual mode of treatment of cancer has until recent years been the direct method of removing the organ containing the growth together with the surrounding tissues and the lymphatic drainage area. The indirect attack on cancer was first introduced by Beatson (1896) using oöphorectomy for the treatment of mammary cancer and later by Huggins and Hodges (1941) using orchidectomy to produce a remission in cases of malignant prostate. This indirect attack has now been carried a stage further by the use of adrenalectomy. The purpose of the indirect attack upon cancer is to bring about a change in the *internal hormonal environment* of the malignant cells, with the object of bringing about their atrophy. No method is yet known whereby we can produce an alteration of this hormonal environment favourable to normal cell growth and unfavourable to malignant cell proliferation except by the relatively crude method of the ablation of the appropriate gland. Further study to measure hormonal levels and to devise methods to modify them is required.

I have dealt here principally with the relatively new procedure of bilateral adrenalectomy and its place in the indirect attack upon cancer of the breast and of the prostate.

The results of adrenalectomy in my series support the claim of Huggins and his co-workers that in some patients with advanced mammary cancer, a major remission as shown by clinical evidence of regression of a primary growth or of cutaneous, hepatic, or cerebrospinal metastases, and by radiographic evidence of improvement of skeletal and thoracic deposits, can follow the operation of bilateral adrenalectomy and bilateral gonadectomy. Other workers have reported similar results (Fergusson, 1954; Cade, 1954).

There does not appear to be any histological criterion for the selection of cases which will regress after adrenalectomy; in this series a response has occurred not only in cases having an adenomatous or alveolar structure, but also in cases of spheroidal-celled carcinoma and in cases having a mixed histological structure, partly alveolar, partly anaplastic. The alveolar type of cancer regarded by Huggins and Das (1953) as being especially favourable for adrenalectomy is shown in *Fig.* 101, a section taken from a case in which there was a remission of eight months following operation.

There is no known method yet available for selecting those cases which will respond to adrenalectomy, and until one is found we are justified in submitting to operation all patients who are reasonably fit. Pearson and others (1954) believe that in cases having skeletal metastases which have been submitted to operation, pre- and post-operative studies of the urinary calcium will give an accurate idea of the prognosis following operation. In cases with osseous metastases, calcium from the breaking-down bone is excreted in the urine in excess of

normal; if the patient is placed on a low-calcium diet there may be a considerable negative calcium balance with a high calcium level in the urine. Following adrenalectomy, they have found in cases which have later had a regression a reduction of the urinary calcium excretion to extremely low levels. Administration of ethinyl œstradiol daily by mouth was followed by a prompt elevation of the urinary calcium, and the subsequent withdrawal of the œstradiol was followed by a further fall in urinary calcium. The changes in the blood and the urinary calcium, in a case in my series, in which no clinical regression followed adrenalectomy, is shown in *Fig.* 102. There was a slight temporary fall of the urinary calcium and of the serum calcium (both of which were raised above normal), after operation, but pre-operative levels of urinary calcium were quickly restored.

After a variable length of time, cases which have had a regression, relapse; the operation appears to be a temporary palliation only. The reason for the final relapse after adrenalectomy is not yet understood. One suggestion is that the tumour, hitherto œstrogen-dependent, now becomes autonomous. We cannot as yet trace the causes of such a change though this theory may well be true. Another suggestion is that following adrenalectomy there is a hypertrophy of accessory cortical adrenal tissue which is present in the form of adrenal rests, and which escapes observation at operation. That accessory adrenals are fairly common is supported by the work of Graham (1953), who found them to be present in 32 of 100 autopsies, of an average size of $7 \times 4 \times 3$ mm. A clinical test in which cortisone is withdrawn in an adrenalectomized patient to see if the patient can live without substitution therapy, if negative does not necessarily imply that there is no accessory adrenal cortical tissue; a small amount of such tissue may be inadequate to sustain normal adrenal mineralo-corticoid function, though adequate to stimulate a malignant growth.

CONCLUSION

The field that I have attempted very briefly to survey, of the indirect approach to the cure of cancer, appears to be a hopeful one. In the last few years much that is new and useful has been learnt. Further progress demands a greater knowledge of the methods of detection, and of the quantitative estimation of hormones and of steroid substances, and also a correlation of the various patterns of these substances in the blood and in the urine with the behaviour of the malignant growth and with its response to various measures designed to give relief. But the work of the last few years may well have been an important milestone in the ultimate cure of cancer.

Since this lecture was given, work relating to mammatrophin and mammary growth has been published by Geoffrey Hadfield (1956). A further paper published by Emerson and Jessiman (1956) also describes methods by which hormone dependency of tumours may be evaluated.

Acknowledgements.—The first half of the adrenalectomy cases of this series was done as part of a Medical Research Council investigation into adrenalectomy for the treatment of cancer; I desire to thank the Medical Research Council for making the supplies of cortisone available.

I wish to thank Dr. G. M. Bonser and Dr. J. W. Jull, of the Department of Cancer Research of the University of Leeds, for helpful criticism in the preparation of this paper; and Mr. M. C. Oldfield for permission to include in my oöphorectomy cases some cases which he has operated on; Mr. F. P. Raper for permission to include in the series some cases of adrenalectomy for malignant prostate and three cases of oöphorectomy; Dr. J. R. Nuttall and my surgical colleagues at the Leeds General Infirmary for allowing me to quote the late results of mammary cancer treated by stilbœstrol and testosterone; my anæsthetists, Dr. G. Harrison and Dr. R. C. Lawrence; Miss M. Hart for invaluable help in collection of the clinical material.

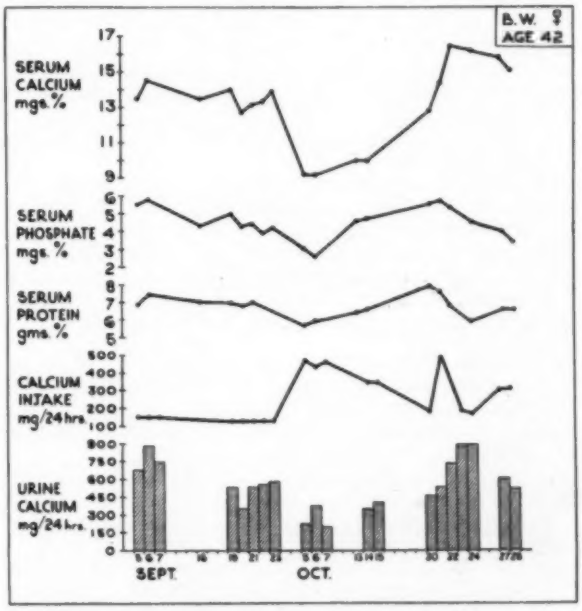


FIG. 102.—Calcium studies in a patient with extensive osseous metastases. (Pre-operatively the serum calcium was raised and the urinary calcium was high. Operation (Oct. 23, 1955) was followed by temporary fall in the serum calcium and in the urinary calcium, but there was a rapid return to pre-operative levels. No clinical response.)

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EXPERIMENTAL SURGERY

MUCOSAL REPAIR IN THE RECTUM

By R. J. O'CONNOR, London

In a previous publication (O'Connor, 1954) it was recorded that, following destruction by the local application of silver nitrate, the mucous glands of the large intestine in mice did not regenerate. In these experiments the underlying muscle coats were destroyed producing a complete breach in the bowel wall which became closed by the formation of fibrous tissue. It remains a possibility, therefore, that the failure of the mucous glands to regenerate might, in part at least, be ascribed to the absence of muscle coats. Experiments have therefore been designed to investigate the regenerative capacity of the mucosa of the large bowel of mice when localized areas are resected leaving the main muscle coats intact. The lesions have, in addition, been studied to determine the extent to which such defects in the mucosa are closed and the factors concerned.

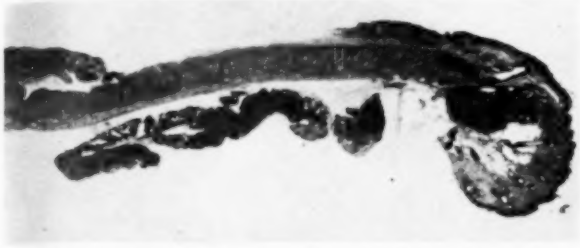

Fig. 103.—Immediately after operation. Muscularis mucosæ and submucosa removed with mucosa. Stain, hæmatoxylin and eosin. (× 15.)

MATERIAL AND METHODS

The mice were adults of laboratory stock and both sexes were used without noticeable differences in the results. After being anæsthetized with ether the animals were tied down on their backs. By suitable retraction at the anal verge the dorsal wall of the anal canal and lower rectum was exposed for 6–8 mm. so that the mucocutaneous junction was clearly seen. From the dorsal wall an area of mucosa about 3 mm. in its craniocaudal length was resected, care being taken to leave undisturbed a strip of mucosa between the caudal border of the lesion and the mucocutaneous junction. In width the resected area involved about one third of the circumference of the bowel.

Fig. 104.—Bowel surface 24 hours after operation. Muscle coats intact. (Specimen fixed in formalin.) (× 7·5.)

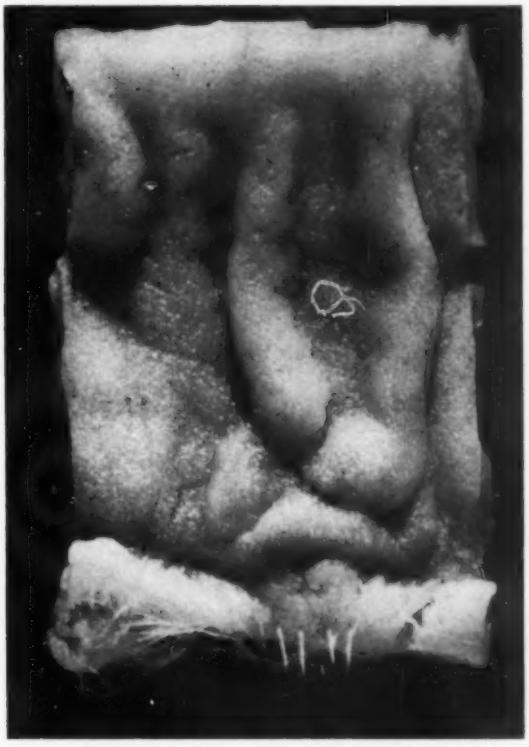

Fig. 105.—Bowel surface 44 days after operation. Muscle coats intact. (Specimen fixed in formalin.) (× 7·5.)

A second series of experiments were performed in which a similar area of mucosa was resected together with the underlying muscle coats, exposing the sphincteric striated muscle and the connective

tissue lying between the bowel and the anterior aspect of the vertebræ. From both operations the animals recovered without incident and were sacrificed at various intervals. The lesions were then examined macroscopically and by making longitudinal sections.

RESULTS

1. After leaving the Main Muscle Coats Intact.—

The lesion inflicted. This is illustrated in *Fig.* 103. The submucosa and muscularis mucosæ have been removed with the mucosa, thus exposing the underlying circular muscle to the lumen of the bowel. The lesion lies over a sphincter of striated muscle which, when the bowel was removed for section, was not always retained and therefore does not appear in some of the sections illustrated. Near the muco-cutaneous junction, the structure of the mucosa becomes slightly modified; consequently the histological changes in the edges of the lesion following resection were studied at its cranial border where the structure of the bowel wall was identical with the more proximal colon. There was, however, no discernible difference in the behaviour of the mucous membrane at the cranial and caudal borders of the lesion.

Macroscopic Examination of the Lesions.— By such examinations the area of the lesion could be compared at different times. Immediately after operation the amount of stretching required to perform the resection obscured its size so that, for comparative purposes, this was best determined 24 hours after operation. The area denuded of mucosa is then covered with fibrinous exudate (*Fig.* 104). No attempt was made to compare accurately the size of the lesion at different stages, but during the fourth week lesions were reduced in size by about half, and in 6–10 weeks they became reduced to small residual ulcers, or could only be detected macroscopically by abnormalities in the mucosal folds (*Fig.* 105). Although, in different mice, the rate of reduction in size varied considerably, it progressed without interruption and no cases were observed in which the lesion increased in size.

Microscopic Examination of the Lesions.—After four days considerable fibrinous exudate remains on the exposed surface of the circular muscle layer, in the substance of which there is an inflammatory

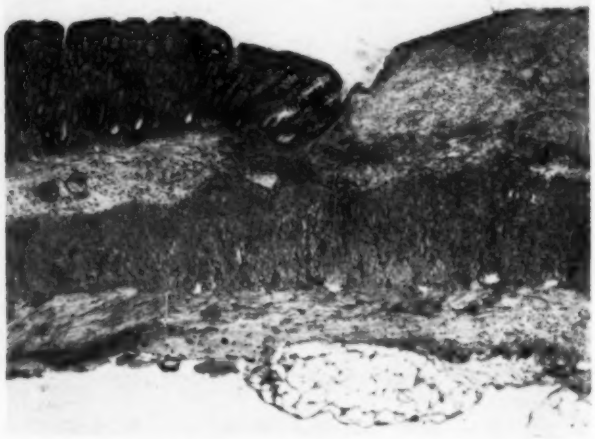

FIG. 106.—Cranial border of lesion 4 days after operation. Slight epithelial outgrowth over the fibrinous exudate on the surface of the lesion. Stain, hæmatoxylin and eosin. (× 36.)

FIG. 107.—Cranial border of lesion 8 days after operation. Spread of inflammatory reaction into submucosa. Stain, hæmatoxylin and eosin. (× 48.)

FIG. 108.—Cranial border of lesion 12 days after operation. Outgrowth of epithelial cells over the organized exudate. Stain, Masson's trichrome. (× 48.)

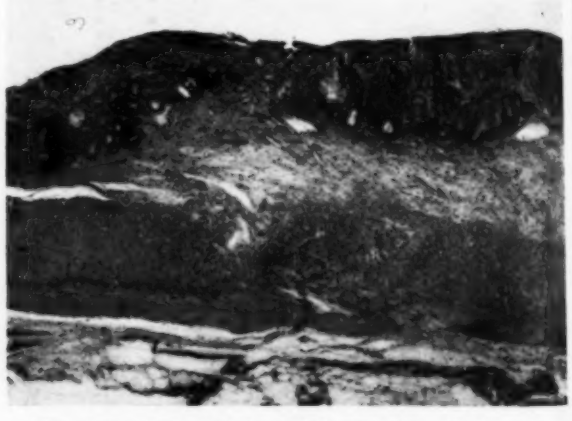

FIG. 109.—Lesion 36 days after operation. Contact of mucosal edges. Stain, hæmatoxylin and eosin. (× 36.)

reaction (*Fig.* 106). However, neither at this nor any subsequent stage does the reaction spread beyond the circular into the outer longitudinal muscle layer. At this stage there is also a very slight epithelial outgrowth, derived from the persisting mucous glands, onto the surface of the exudate.

By the eighth day the surface exudate is becoming organized and the inflammatory reaction in the circular muscle layer more pronounced (*Fig.* 107).

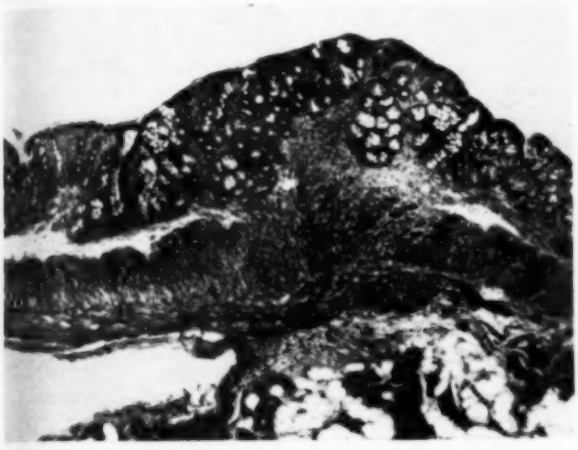

FIG. 110.—Lesion 46 days after operation. Further approximation of mucosal edges. Note 'septum' of connective tissue extending from circular muscle layer through the submucosa and mucosa. Retracted edge of muscu' ris mucosæ visible at extreme left. Stain, Masson's trichrome. (× 33.)

Simultaneously the inflammatory reaction extends for a short distance between the persisting mucosa and the circular muscle coat, giving the appearance of uniting both and thus sealing off the submucosa and lamina propria from the lumen of the bowel. From this union the muscularis mucosæ appears, in *Fig.* 107, to be excluded and at later stages is seen to have retracted considerably from the mucosal edge (*Fig.* 110). This retraction of the muscularis mucosæ might be responsible for the reorientation of the mucous glands which, at the edge of the lesion in *Fig.* 107, lie horizontally rather than vertically to the muscle layer.

During the second week the inflammatory process in the circular muscle layer leads to an increase in the number of fibroblasts, without, however, involving the longitudinal layer (*Fig.* 108). The exudate on the surface of the circular muscle has become reduced and more organized, and over it the outgrowth of epithelium from the persisting mucosa extends to reach the maximum extent observed. This is, however, never greater than 500–600 μ. In the outgrowth, both at this and subsequent stages, dividing cells or other evidence of new gland formation were never seen. In *Fig.* 108 the artefactual separation of the mucosa from the circular muscle layer demonstrates the strength of the union between the mucosal edge and the fibrous reaction which develops in the exudate and circular muscle. It is by this union that one mucosal edge is connected with the opposite.

By the seventh week, lesions have become greatly reduced in size and, in section, present the appearance of *Fig.* 109. Superficially the edges of the mucosa have come into contact by means of the epithelial outgrowths. Deeper in the mucosa, however, the edges of the lesion remain separated by newly formed fibrous tissue, which extends through the submucosa into the circular muscle layer. In the succeeding weeks this separation is narrowed and the mucosal edges become approximated throughout their whole thickness, remaining separated, however, by the connective tissue in the mucosa which has narrowed to form a fibrous septum

FIG. 111.—Lesion 66 days after operation. The circular and longitudinal muscle coats resected with the mucosa. Mucosal edges in close contact but separated by a fibrous septum. (Cf. *Fig.* 110.) Stain, Masson's trichrome. (× 57.)

(*Fig.* 110). The fibrous tissue in the submucosa and circular muscle has similarly contracted. The edge of the muscularis mucosæ, however, does not participate in this approximation, and becomes more and more separated from the mucosal edge. It is seen at the extreme left of *Fig.* 110.

2. After removing the Muscle Coats with the Mucosa.—After the production of this complete breach in the bowel wall, it became filled with fibrinous exudate and on macroscopical examination of the mucosal surface could not be distinguished from lesions of an equivalent age in which the muscle layers had been retained. By organization of this exudate the gap in the muscle layers was filled and became adherent to the anterior surface of adjacent vertebræ from which at later stages, the bowel had to be dissected. The changes in the mucosa, as studied in longitudinal section, closely resembled those in lesions with intact circular and longitudinal muscle coats, and the gap in the mucosa closed at a similar rate. *Fig.* 111 illustrates a lesion made ten weeks previously in which the muscle coats were removed with the mucosa. The gap in the former persists but over it the mucosal edges have come together and, as in *Fig.* 110, the line of contact is indicated by a fibrous septum, which extends from the mucosa, through the submucosa but which ends in the fibrous union between the edges of the muscle layer.

DISCUSSION

In the presence of the main muscle coats, the only evidence of mucosal regeneration found was an epithelial outgrowth of the sort illustrated in *Figs.* 106, 108. Since in it neither dividing cells nor

evidence of formation of mucous glands were found it is to be concluded that the regenerative capacity of the mucosa is no greater in the rectum, with the muscle coats intact, than in more proximal colonic regions when all layers, including the muscular, were destroyed by the local application of silver nitrate (O'Connor, 1954). A contrast between the regenerative capacity of the mucosa of the large and small intestine is thus confirmed, for resection of the ileal mucosa in the cat, leaving the muscle layers intact, is followed by complete regeneration of all mucosal elements. (McMinn and Mitchell, 1954.)

It is apparent therefore that the closure of the mucosal gap observed in these experiments cannot be ascribed to the formation of new mucosa and must be due therefore to the mechanical approximation of the mucosal edges. In this approximation it appears that the muscle coats do not play an essential part. The muscularis mucosæ retracts considerably from the approximating edges (*Fig.* 110) and the edges come together just as well as when the muscle coats are removed from the site of the lesion along with the mucosa (*Fig.* 111). It is to be concluded, therefore, that the main factor in closing the gap in the mucosa is the formation and contraction of fibrous tissue which forms in the lesion. Certain similarities are found in biopsy wounds in the human colon which have been studied by Lumb and Protheroe (1955), when biopsies were performed 2–12 days before colonic resection. They noted the contraction of fibrous tissue in the lesion and the epithelial outgrowth from persisting mucous glands. As in the mouse no evidence of new gland formation was noted in these outgrowths.

In the mouse it can be suggested that *Fig.* 107 represents an important stage in the closure of the lesion by fibrous tissue formation. The inflammatory reaction extends for a short distance into the submucosa causing an adhesion between the persisting mucosa and the underlying circular muscle layer. To this adhesion two consequences can be attributed. Firstly, the submucosa and lamina propria are sealed from the bowel contents and the spread of infection along them prevented. No evidence of any such spread was, in fact, observed in any lesion studied. Secondly the mucosal edge of the lesion becomes attached to the fibrous tissue developing in the circular muscle layer (cf. *Fig.* 108) and thereby is attached to the opposite mucosal edge. Such a fibrous attachment, irrespective of the presence or absence of the muscle layers, could cause an approximation of the mucosal edges by its contraction, and produce the similarities of mucosal approximation found in the presence and in the absence of the main muscle coats.

In the present experiments and in those reported previously (O'Connor, 1954) lesions of different depths have been studied in the large bowel of the mouse. Previously it was recorded that if, following the application of silver nitrate, the bases of the glands were left intact over undamaged muscularis mucosæ, complete regeneration followed. In the present experiments, when mucosa and muscularis mucosæ are both resected, mucosal regeneration does not occur but the gap becomes closed by the approximation of the mucosal edges. Thus neither lesion undergoes the extension characteristic of the ulcers of human ulcerative colitis. The possibility can therefore be considered that, for an ulcer progressively to increase in area, it is required that the mucous glands be completely destroyed and that the muscularis mucosa remain intact or comparatively so.

The presence of the muscularis mucosæ might, in these circumstances, interfere with the formation of the inflammatory union between the mucosa and circular muscle layer illustrated in *Fig.* 107. As a consequence infection might not be excluded from the lamina propria so that it could undermine and destroy further mucous glands—a process by which the ulcers of ulcerative colitis enlarge (Brooke, 1953). Further, an intact muscularis mucosæ might interfere with the formation of the fibrous connexion, illustrated in *Fig.* 108, which passes through the substance of the circular muscle layer, from one mucosal edge to the opposite. On this fibrous connexion, it has been concluded, the approximation of the edges depends.

Some evidence can be cited in favour of such an 'initial' lesion in ulcerative colitis. Firstly, in the bases of the ulcers of this disease, the muscularis mucosæ can usually be found and frequently it is hypertrophied (Warren and Sommers, 1954). Secondly, complete destruction of mucous glands, leaving the underlying muscularis mucosæ intact, would be the expected consequences of the rupture of 'crypt abscesses' described in ulcerative colitis by Warren and Sommers (1949). Thirdly, even an area of mucosal destruction no bigger than that produced by the rupture of a single crypt abscess might, owing to the inability of the colonic mucosa to replace lost glands, become progressive if it allowed infection to enter the lamina propria, superficial to the muscularis mucosæ, and destroy more glands by 'undermining' them.

SUMMARY

Areas of mucosa have been resected from the rectum of mice leaving intact the circular and longitudinal muscle layers. Under these conditions no regeneration of mucous glands was observed.

The area so denuded of mucosa became covered by approximation of the mucosal edges of the lesion.

This approximation took place equally as well when the muscle coats were removed with the mucosa as when they were retained, so that the main factor in approximating the mucosal edges is considered to be the contraction of the fibrous tissue which results from the inflammatory reaction in the lesion.

The mechanism of the closure of gaps in colonic mucosa is discussed, and the suggestion made that complete destruction of the mucosa, leaving the muscularis mucosæ undamaged, or only partially damaged, may be a condition necessary for the lesion to increase in size. This suggestion is considered in relation to the pathogenesis of human ulcerative colitis.

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THE INHIBITORY ACTION OF A LOCALLY APPLIED ANTIHISTAMINE ON CANINE GASTRIC SECRETION INDUCED BY PERIPHERAL PARASYMPATHETIC STIMULATION

BY A. W. KAY AND A. P. M. FORREST
THE UNIVERSITY DEPARTMENT OF SURGERY, WESTERN INFIRMARY, GLASGOW

IN a previous paper we have shown that in Heidenhain pouch dogs the secretion of acid in response to histamine can be prevented by irrigating the pouch with an antihistamine (promethazine). We considered this inhibition to be due to specific antagonism between histamine and the antihistamine: but Robertson and Grossman (1952) in similar studies have attributed it to damage of the gastric mucosa caused by the direct irritant action of the antihistamine.

In the present paper we present similar studies in which the pouch secretion has been provoked not by histamine but by carbaminoyl-β-methyl choline chloride, which stimulates pepsin as well as acid production. We shall show that the anti-histamine selectively inhibits the acid production. We believe that this supports the view that its action is not a non-specific effect but a pharmacological antagonism.

METHOD OF STUDY

Four dogs with separated pouches of the stomach (Heidenhain type) were used. Animals were fasted for a period of 16 hours before each test. Secretion of juice, rich in acid and pepsin, was stimulated by carbaminoyl-β-methyl choline chloride (Mecothane—Savory & Moore), given by subcutaneous injection in a dose of 0·25 mg. quarter-hourly for a period of 2½ hours. During this period juice was collected at 15 minute intervals, the volume measured in ml., and the concentration of free hydrochloric acid determined by titration with decinormal sodium hydroxide, using Topfer's solution (*p*-dimethyl aminoazobenzine) as indicator. From these values, the output of hydrochloric acid for each 15 minute period was calculated in milliequivalents. During each test in each dog specimens of hourly or half hourly juice were obtained by pooling aliquots of each 15 minute collection. The concentration of pepsin in these pooled samples was estimated by the method of Hunt (1948) using dried human serum as substrate. The peptic activity has been expressed in milligrammes of tyrosine-like substances liberated from the substrate per ml. of juice, and the product of the hourly or half-hourly volume of juice, and its peptic activity represents the output of pepsin in mg. of tyrosine equivalents per hour or half hour.

The effect of locally applied antihistamine on the secretory response to mecothane was determined by irrigating the pouch with a solution of promethazine hydrochloride (6 mg. per ml. 0·9 per cent saline) for a half hour period before commencing the mecothane injections. The method of irrigation was as previously described (Kay and Forrest, 1956). Three tests were performed on each of the 4 dogs. In three control experiments on each animal, the pouch was irrigated with 0·9 per cent saline alone.

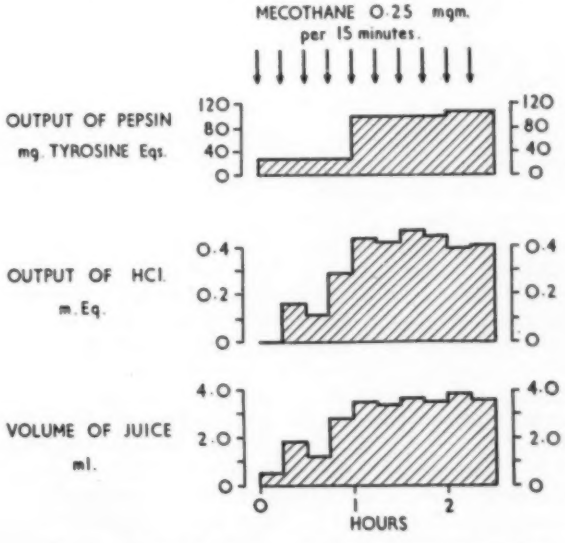

FIG. 112.—The secretory response of a separated gastric pouch in a dog to repeated subcutaneous injections of carbaminoyl-β-methyl choline chloride.

In the control studies the acid and pepsin responses to repeated subcutaneous injections of mecothane reach and maintain a steady level after four injections (*Fig.* 112). The output of the pouches during the final 90 minutes of the test thus gives a reliable indication of the effect of mecothane stimulation. The logarithms of these outputs were used for a statistical analysis, the probable significance of the difference between the means of the control and promethazine tests being estimated by an analysis of variance.

RESULTS

In all twelve tests after irrigation of the pouches with promethazine the acid secretion was abolished, but the volume of fluid secreted and likewise its

pepsin content was influenced only to a smaller degree (*Table I, Fig.* 113). The mean volume was 67 per cent of the control values. Statistical analysis allows the assumption that this value is of significance ($P < 0.01$).

The pepsin output was reduced in three of the dogs, with an overall mean reduction to 56 per cent of the control value. This reduction in pepsin output is not of significance.

Table I.—THE EFFECT IN DOGS WITH HEIDENHAIN POUCHES OF LOCALLY APPLIED PROMETHAZINE HYDROCHLORIDE ON THE SECRETORY RESPONSE TO STIMULATION BY CARBAMINOYL-β-METHYL CHOLINE CHLORIDE

	Volume Juice ml.		Output HCl mEq.		Output Pepsin mg. Tyrosine	
	Control	Promethazine	Control	Promethazine	Control	Promethazine
Dog A	25·3	9·7	3·256	0	596·8	146·6
Dog B	7·8	6·6	0·428	0	95·5	42·2
Dog C	8·0	6·0	0·501	0	170·2	73·9
Dog D	14·1	9·8	1·028	0	104·4	115·6

(Each figure represents the mean of three tests.)

DISCUSSION

We have shown that promethazine, applied locally to Heidenhain pouches in dogs, differentially affects the volume, acidity, and pepsin content of the secretion provoked by carbaminoyl-β-methyl choline. This observation refutes the suggestion that the action of the antihistamine is a non-specific one.

We have shown that promethazine has a pronounced action on the secretion of acid which we believe is due to specific antagonism to histamine. Its less marked action on the secretion of pepsin may be secondary to the fall in acid secretion, for, according to Babkin (1950), acid secretion from the depths of the gastric glands flushes out pepsin stagnating within the tubules so, conversely, inhibition of acid flow will lead to an apparent reduction in pepsin. Alternatively, it may be that the pepsin-secreting cells are also, to a slight degree, under histamine control (Bucher, Ivy, and Gray, 1941), so the reduction in pepsin secretion may also be due to a specific anti-histamine effect.

The observation that acid secretion in response to carbaminoyl-β-methyl choline can be abolished by an antihistamine is evidence that this cholinergic drug acts, not directly on the acid-secreting cells, but through the mediation of histamine.

SUMMARY

In dogs with Heidenhain pouches, we have studied the effect of a locally applied antihistamine on the volume, acid, and pepsin output induced by repeated subcutaneous injections of carbaminoyl-β-methyl choline.

While the antihistamine caused some reduction in the volume of juice and in the output of pepsin in response to this stimulus, the secretion of acid was reduced to zero.

It is concluded that the antihistamine acts as a specific antagonist to histamine and not as a non-specific irritant.

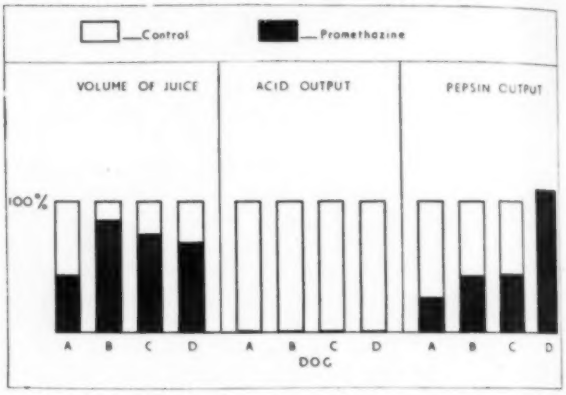

FIG. 113.—The effect of promethazine hydrochloride on the output of juice, acid, and pepsin, from separated pouches of the stomach stimulated by carbaminoyl-β-methyl choline chloride. In each dog each output represents the mean of three tests, expressed as the percentage of the control values.

We are indebted to Professor Weipers and his staff of the Veterinary Hospital for their assistance in the provision and care of the dogs. We also wish to thank Dr. R. A. Robb of the Department of Statistics for his analysis of the data.

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SHUNT ARTERIAL HOMOGRAFTS

AN EXPERIMENTAL STUDY WITH A NOTE ON CLINICAL IMPLICATIONS

By G. E. MAVOR

SENIOR SURGICAL REGISTRAR, ABERDEEN ROYAL INFIRMARY, AND FELLOW IN SURGERY, ROCHESTER UNIVERSITY MEDICAL SCHOOL, N.Y., U.S.A.

In the direct surgery of the occluded peripheral artery, published series have almost exclusively employed an end-to-end anastomosis method, whether the replacement material has been autogenous vein (Julian, Grove, Dye, Olwin, and Jordan, 1952), homologous artery (Hufnagel and Eastcott, 1950, 1951, 1952; Fontaine and Hubinot, 1950; Rob and Eastcott, 1953) or a plastic substitute (Hufnagel, 1955). An arterial homograft has been most often used, although the difficulties of procurement and storage remain as serious disadvantages. The immediate results with arterial homografts have been satisfactory, although an early post-operative thrombosis rate of about 20 per cent is usual (Rob and Eastcott, 1953). Of more significance is the growing experience that late thrombosis up to one year may reach 75 per cent of those grafts patent at the time the patient leaves hospital (Linton, 1955). This is a figure paralleled by the late thrombosis rate in autogenous vein grafts inserted by end-to-end suture (Fontaine, Riveaux, Kim, and Kiey, 1952), so that the nature of the graft is possibly not of importance. The explanation may lie in fibrosis at the suture line leading to narrowing of the lumen, a narrowing which is always initially present in some degree, however expertly the anastomoses are fashioned.

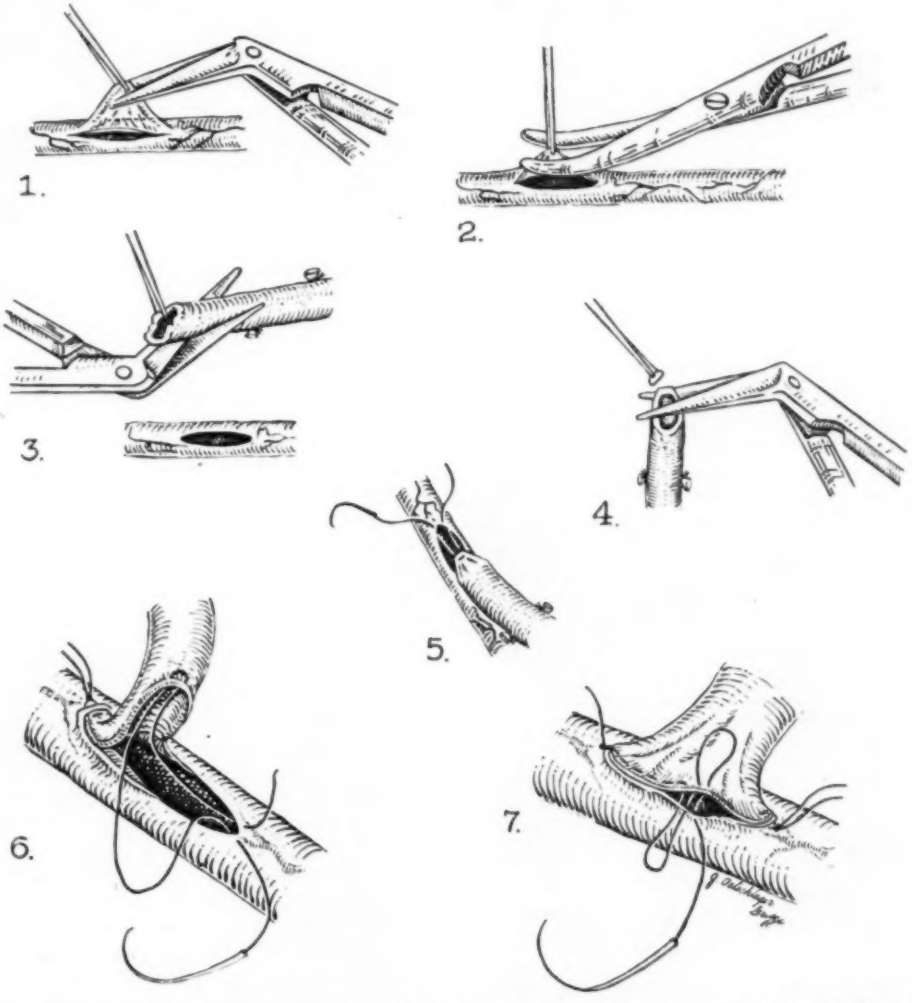

FIG. 114.—Technique of anastomosis. The adventitia is cleared from the host artery (1), and the longitudinal incision converted to an ellipse (2). The arterial homograft cut is obliquely (3), and the end squared (4). This permits good 'seating' of the proximal mattress suture (5). The distal mattress suture is then placed (6). A continuous eversion suture (7) is used to complete the anastomosis.

Little attention has been paid to the use of shunt or by-passing arterial homografts, as it has been the general belief that the turbulence in blood-flow in such a graft would lead inevitably to early thrombosis (Rob and Eastcott, 1953). Nevertheless, in the surgery of segmental lower limb main vessel occlusion, the successful employment of such a method has obvious advantages, the most important being the preservation of collateral channels. Accordingly, the feasibility of arterial reconstruction by this means has been examined, the emphasis in this study being on the technique of anastomosis and the early results.

EXPERIMENTAL STUDY

Preparation of Grafts.—In all cases arterial homografts were used. After a preliminary period of 24 hours in streptomycin-saline solution at 4° C., the grafts were frozen in liquid nitrogen and stored at − 20° C. The period of storage before use varied from 2 days to 1 month.

Table I.—Details of Average Diameters of Host Artery and Long Arterial Homografts (Length 16 cm.) in 23 Dogs

	Proximal Anastomosis	*Distal Anastomosis*
Host artery	Right external iliac artery 5–6 mm.	Distal femoral artery 3·5–4 mm.
Arterial homograft	Right external iliac artery 5–6 mm.	Midfemoral artery 4–5 mm.

Methods.—Two groups of dogs were used in this study. Group I consisted of 23 dogs in which shunt homografts of an average length of 16 cm. were inserted from the proximal external iliac artery to the distal femoral artery in the thigh. The details of diameter of both host artery and homograft are given in *Table I*. The operation was carried out through two incisions and the area of the inguinal ligament tunnelled so that the graft lay alongside the host artery which was tied at two points below the inguinal ligament and at one site above it, in some cases just distal to the origin of a large supra-inguinal branch. In this way thrombosis of the host artery with a large collateral vessel below the proximal anastomosis was simulated.

Group 2 consisted of 16 dogs in which the shunt homograft was inserted entirely below the inguinal ligament, the host artery being doubly ligated between the anastomoses. The average length of graft was 8·5 cm. and the details of diameter are given in *Table II*.

Table II.—Details of Average Diameters of Host Artery and Short Arterial Homografts (Length 8·5 cm.) in 16 Dogs

	Proximal Anastomosis	*Distal Anastomosis*
Host artery	Proximal femoral artery 4–5 mm.	Distal femoral artery 3·5–4 mm.
Arterial homograft	External iliac artery 5–6 mm.	External iliac artery 5–6 mm.

Anastomosis Technique.—In all cases a standard anastomosis technique was employed (*Fig.* 114), using five zero arterial silk on a round-bodied needle. To control bleeding, the anastomosis was wrapped in gelatin sponge, which was later removed in some cases.

Post-operative Follow-up.—At the end of the third post-operative week, a record was made of the patency of the graft and arteriography carried out (*Figs.* 115, 116). Thereafter the dogs were sacrificed at varying intervals up to six months, and the graft examined. In Group I 6 dogs with patent grafts and in Group II 3 were observed for six months before sacrifice.

RESULTS

The results are shown in *Table III*. In Group I 7 grafts were thrombosed within three weeks post-operatively. One failure was due to hæmatoma formation around the graft, and a second to wound dihescence with infection and secondary hæmorrhage. In 5 cases it was considered that thrombosis might be related to the constricting effect of the inguinal tunnel. Some attempt at dilatation and widening of the inguinal canal was made in all cases, in some by partial incision of the deep aspect of the ligament. In one case a prevascular hernia developed. However, inguinal constriction remained a serious problem in the dog, and probably accounted for the poor immediate results in Group I as compared to Group II, where the graft was located entirely in the thigh.

Table III.—Early Results in 39 Shunt Arterial Homografts

	Dogs	*Patent (at 3 weeks)*
Long shunt homograft (16 cm.)	23	16
Short shunt homograft (8·5 cm.)	16	15

In Group II thrombosis in one case was regarded as due to narrowing of the host artery by the tying of a too widely placed proximal mattress suture: this was noted after the completion of the anastomosis. This constriction undoubtedly occurred more often (*Fig.* 117) and is an important technical error to be avoided in small lumen arteries.

COMMENT

There are certain inherent advantages in an end-to-side anastomosis as opposed to an end-to-end one. By obliquely cutting the graft, the anastomosis can be maintained at a workable size, which in this study has been 12 mm. in its long diameter, much larger than either the host artery or the homograft. The fact that the host artery may be of very small calibre thus presents no problem. This is best exemplified by the anastomosis at the distal femoral artery, where the host artery was usually 3·5 or 4 mm. in diameter (*Fig.* 118). This means that an exact matching in calibre between host artery and homograft is unnecessary, and indeed there may be some advantage in having the graft of larger calibre than the host artery as regards the delivery of blood to the periphery at higher pressure and better volume flow than normal.

It is felt that the ellipse in the host artery should be fashioned in such a way that allowing for suturing the diameter of the host vessel is fully utilized at the anastomosis, so that there is little possibility of the anastomosis becoming slot-like. A further technical point is the squaring of the apex of the obliquely cut graft (*Fig.* 114). This allows satisfactory bedding of the proximal mattress suture and

facilitates the fashioning of the proximal corner of the anastomosis.

It is apparent that in such an anastomosis the suture line represents the widest part of the union. This is the exact reverse of the circumstances prevailing with an end-to-end anastomosis method, where the suture line is inevitably the narrowest area. As regards the late thrombosis rate, which may be related in many cases to fibrosis and further narrowing at the suture line, this fundamental difference in the two methods may be significant, explaining in the case of shunt grafts the absence of late thrombosis in this study up to six months, and the low clinical incidence reported by Linton (1955).

FIG. 115.—An arteriogram of a 16 cm. shunt arterial homograft. Some tortuosity is present.

FIG. 117.—An arteriogram of a short shunt arterial homograft, showing a constricted host artery just proximal to the proximal anastomosis. The distal anastomosis is satisfactory. The homograft is considerably larger than the host vessel.

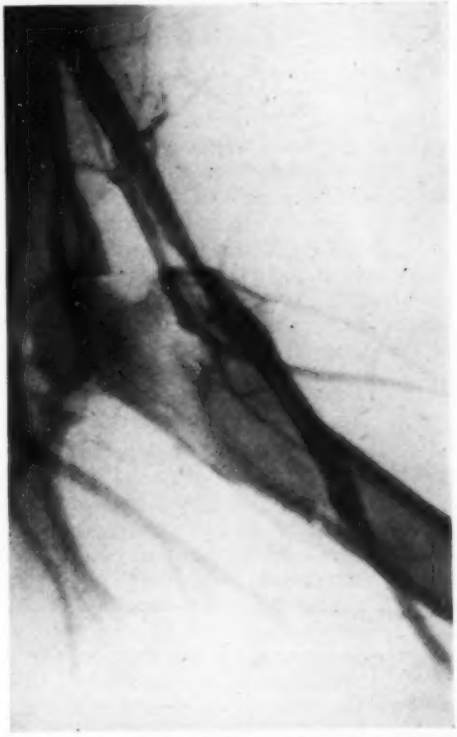

FIG. 116.—An arteriogram of an 8·5 cm. shunt homograft. There is very slight narrowing of the host artery just proximal to the proximal anastomosis. The distal anastomosis appears satisfactory.

FIG. 118.—Distal anastomosis between the homograft and the host vessel, which has been ligated just proximal to the site of anastomosis. The distal host vessel is 4·0 mm. in diameter. The discrepancy in size between homograft and host artery can be seen.

CLINICAL IMPLICATIONS

It is important that such a method of anastomosis is feasible, because many clinical advantages accrue from its use. These include the limited exposure necessary, and the avoidance of an extensive arterial resection. It should also be mentioned that there is a place for end-to-side anastomosis in the distal

anastomosis of an aortic bifurcation graft inserted in the treatment of an aneurysm, where extension of the aneurysm into common, internal or external iliac arteries might raise difficulties if end-to-end anastomosis is attempted. However, there is no doubt that the greatest advantage of the method described in this study lies in the preservation of collateral vessels. In segmental occlusion of the main artery of the lower limb, which is secondary to atheroma, the important collateral vessels are the profunda femoris proximally in femoral occlusion, and the vessels at the adductor magnus opening area, which limit distal extension of a femoral thrombosis for a time and proximal extension of a popliteal thrombosis (Mavor, 1955). In fact if arterial resection and graft replacement by end-to-end anastomosis were to be undertaken in all cases of segmental occlusion, one anastomosis would be at the adductor magnus opening site in over 90 per cent of cases (Mavor, 1955). It is apparent then that these collateral vessels are especially vulnerable. Furthermore the preparation of the host vessel for end-to-end suture may entail a short endarterectomy or encroachment on the lumen of a large collateral such as the profunda femoris, both measures calculated to jeopardize a successful result. It has even been proposed in fact that collateral vessels should not be allowed to limit resection and be sacrificed without hesitation in order to gain a suitable site for end-to-end suture. It is doubtful whether this is justifiable as it narrows the margin of safety with which all surgery should be concerned. By the use of the shunt method, all collaterals are preserved, and the most suitable sites for the anastomoses as regards exposure and arterial involvement in disease can be selected.

SUMMARY

1. A series of 39 dogs in which shunt arterial homografts were inserted is presented. The immediate results show a 79 per cent incidence of patency at the third post-operative week.

2. In 9 dogs, there was no late thrombosis up to six months post-operatively.

3. If the shunt graft passes deep to the inguinal ligament, a higher incidence of immediate post-operative thrombosis is to be expected, due possibly to the constricting effect of the inguinal tunnel. This may not be of clinical significance.

4. The technique of anastomosis is described, and the technical advantages of end-to-side anastomosis discussed.

5. The clinical benefits of such a method of arterial reconstitution are noted.

The facilities for this work were provided at the University of Rochester Medical School, Rochester, New York. I wish to thank Dr. W. J. M. Scott and Dr. Earle B. Mahoney for their interest and encouragement. My gratitude is also due to Mrs. M. Metzler for her skilful operative assistance and her expert care of the experimental animals.

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SHORT NOTES OF RARE OR OBSCURE CASES

CHONDROSARCOMA OF THE PUBIC BONE

By DONALD YOUNG, O.B.E., T.D.
CONSULTANT SURGEON, WARRINGTON INFIRMARY

THE infrequency of excision of the pubic bone for chondrosarcoma has encouraged the publication of the following case.

CASE REPORT

HISTORY.—The patient, a man of 34 years, was first seen at Surgical Out-patients in July, 1952. He had noticed a mass in his right groin for a fortnight. The mass felt hard and appeared to be separating his adductor muscles. Pain was referred to the right hip and right knee-joint. A diagnosis of psoas abscess or obstructed obturator hernia was suggested and radiographs of the spine and pelvis were ordered. The radiograph showed no evidence of pathological bone changes in the dorsal spine, but a calcified shadow was seen superimposed on the right os pubis and there appeared to be some periosteal thickening of the pectoneal line (*Fig.* 119).

At operation on July 18, 1952, the lesion was found to be a chondromatous mass and a biopsy specimen was taken. This was reported as a chondrosarcoma. A radiograph of the chest showed no lung pathology and a

further film of the pelvic brim did not show any sign of erosion in the pubic region.

Hindquarter amputation was suggested but the patient preferred to keep his leg. The small tumour was in no way incommoding him and he could walk or run without difficulty.

By December, 1952, the mass had increased in size and he was having pain in the right thigh and knee. A further operation removed a large tumour mass and the obturator nerve was cut.

FIG. 119.—Radiograph of pelvis showing tumour as a calcified shadow superimposed on the right os pubis.

FIG. 121.—Drawing showing mass of tumour and bone removed at operation.

By February, 1954, there was a swelling as large as a newborn baby's head in the right groin, growing down the thigh. A mass could also be felt in the abdomen in the right iliac fossa. The patient agreed to local removal of the tumour and operation was performed on Feb. 23.

AT OPERATION.—A T-shaped incision was made in the right groin with the vertical incision carried down the thigh in the line of the femoral vessels. The pubic bone and ramus were exposed and the latter was cut through with a saw. The retroperitoneal mass arising from the obturator foramen was peeled off the peritoneum. The mass in the thigh was freed from the adductor muscles and dissected off the femoral vessels. After the pubic bone and ischium had been cleared of their attachments and sawn across, the tumour was removed *en bloc* (*Fig.* 120). The large gap in the right groin was closed with interrupted thread suture of fascia and muscle. The skin was closed and a small drain left in the thigh wound because of the looseness of the skin there. A hip spica of 6-in. domette bandage over the dressings completed the operation.

On examination three days after operation it was found that he had developed a scrotal hæmatoma on the

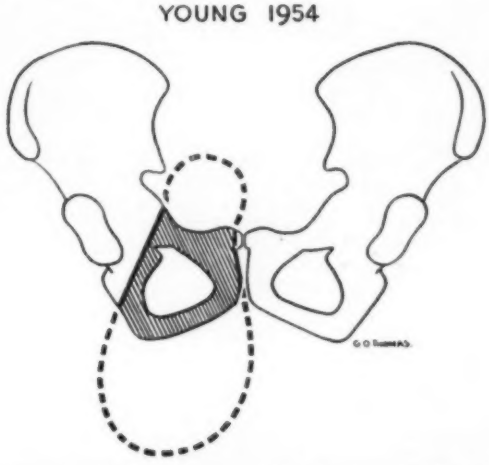

FIG. 120.—Diagram showing position of tumour, and area of bone excised.

FIG. 122.—Radiograph taken post-operatively, showing area of bone excised.

right side. His hæmoglobin was 56 per cent. A blood transfusion was advised but firmly refused by the patient because of religious beliefs; he is a Jehovah Witness. In spite of his low hæmoglobin he made an uneventful recovery.

THE SPECIMEN.—The tumour and bone removed weighed 4 lb. 13 oz. (2192 g.) (*Fig.* 121). It was a pear-shaped mass which measured 16 × 18 × 10 cm. in the thigh and 8 × 11 × 7 cm. in its retroperitoneal extension. The pathologist reported as follows: "It consists of very numerous lobules of hyaline cartilage. The larger ones have become cystic and the smaller ones are at the periphery of the mass. Microscopically it is similar to the earlier biopsy specimen."

PROGRESS.—In two weeks the patient was weight-bearing, using crutches. An X-ray report on March 9, 1954, stated: "The pubic bone on the right side has been removed. There is no evidence of further bony change." (*Fig.* 122.)

When seen in Out-patients on April 30, his general condition was satisfactory. He said he was feeling very well and could walk, sit, and lie down in comfort. There was no pain now, but he was still wearing the hip spica as a support. On July 20 the right groin had healed firmly. There was some thickening along the inguinal ligament but no evidence of a hernia.

On routine examination in December, 1954, a definite nodule of a recurrence of the tumour was felt above the

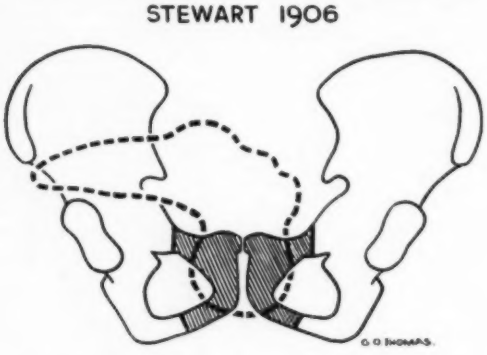

FIG. 123.—Diagram of case described by Stewart (1906). Showing position of tumour and area of bone excised.

inguinal incision. The man was very agile and his general condition was satisfactory. He was advised to come in for removal of the nodule.

At operation on Jan. 10, 1955, four nodules of secondary tumour growth were found—one in the retroperitoneal space, lateral to the external iliac artery, one in the rectus muscle, and two in the external oblique muscles. The histological picture of these recurrent tumours was similar to that of the earlier specimens. One of the tumours, that from the retroperitoneal space, was reported on as follows: "This fragment looks more malignant than any specimens hitherto seen from this patient. Here and there, ill-formed vascular spaces can be found with very thin walls. Mitotic figures, which have hitherto been infrequent, can now be found without difficulty. There is also considerable pleomorphism."

COMMENT

Muir (1951) and Strange (1954) have shown that removal of one pubic bone causes no great disability. Stewart (1906) removed parts of both pubic bones (*Fig.* 123) in the excision of a spindle-cell sarcoma arising from the periosteum on the back of the pubic ramus. King had suggested in 1931 that local removal rather than the more radical methods of treatment would save unnecessary mutilation in the comparatively benign cases. This case confirms the possibility of conserving the leg and the hip-joint when excising sarcoma of the pubic bone. Although on the conclusion of the excision a gap is left through which you may pass your fist, it is interesting to note that in this, and the previously recorded cases, a hernia did not develop at the operation site.

Pathology.—Evans (1956) states that chondrosarcomata may appear as large smooth or lobulated tumours covered by a layer of expanded periosteum; they project into the adjacent soft tissues and proceed to infiltrate. The microscopical appearances of a chondrosarcomatous lesion may resemble those of a benign chondroma so closely that the tumours are histologically indistinguishable. On other occasions the chondrosarcomatous nature of the neoplasm is histologically obvious. In between these two types of structure there are transition forms in which features of malignancy are more or less apparent. Phemister (1930) stated that chondrosarcomata may grow more rapidly than osteogenic sarcomata, producing more bulky neoplasms and giving rise to metastases at a late phase in their evolution and development. Lichtenstein (1952) observed that untreated chondrosarcomata are likely to remain only locally invasive for years. If the tumour had not been completely excised at the initial surgical operation, local recurrence of the lesion in even bulkier form is almost the rule. This case would appear to show that once local recurrence has commenced the tumour spreads rapidly and grows quickly. Lichtenstein agrees that the only form of therapy which offers any prospect of cure in cases of chondrosarcoma is surgery.

SUMMARY

A case of excision of the pubic bone for chondrosarcoma is reported.

1. In spite of late excision by local removal the patient had ten months of normal life before secondary tumours appeared.

2. Removal of one pubic bone does not make the pelvis unstable and hernia following the operation is unlikely.

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URETERITIS CYSTICA

By RICHARD E. SHAW
COVENTRY AND WARWICKSHIRE HOSPITAL

Of recent years a number of papers have appeared in the American literature dealing with proliferative and cystic changes in the mucosa of the upper urinary tract. Little attention has been paid to these conditions in this country, and only a few examples have been recorded.

PATHOLOGY

The bladder mucosa, in response to chronic irritation by infection or mechanical influences, is capable of undergoing cystic or proliferative changes and of developing the faculty of secreting mucus. The changes produced may take a variety of forms—cystitis cystica, cystitis glandularis, leukoplakia, cystitis follicularis, and cystitis emphysematosus—but all these conditions are closely related and one may exist with another. Much attention has been paid to downgrowths of epithelial cells from the mucous lining, entitled ' Brunn's nests ', and there has been a good deal of speculation as to their origin and cause. Most authors agree with Patch and Rhea (1935) in regarding the mucosal changes as a metaplasia due to chronic irritation, and have discarded developmental and other theories. Either infection or mechanical influences may initiate the metaplastic process, but the changes are most frequently seen when both factors are present, as for instance in congenital exstrophy of the bladder, a condition in which they are particularly amenable to study. In other cases the mechanical factor is provided by calculi. The metaplasia may advance a step further and malignancy supervene in the form of adenocarcinoma or squamous-cell carcinoma, depending on the character of the initial changes.

While cystic and glandular changes are fairly common in the mucosa of the bladder, they are much less frequently found in the upper urinary tract, although cystic changes in the ureter were described as long ago as 1761 by Morgagni. Pyelitis glandularis is particularly rare, and Aiken (1955) in presenting an example could find only 6 previous instances. Cystic changes are somewhat less rare, and pyelitis cystica and ureteritis cystica have been described on a number of occasions. It should be appreciated that pyelo-ureteritis cystica is not a pathological entity in itself, but is an end-result of another disease process. The kidney on the affected side is invariably diseased, chronic pyelonephritis and calculi being most frequently found. The cysts are multiple, rarely as large as 0·5 cm. in diameter, and of a yellow or brown colour. The condition may be unilateral or bilateral and may be associated with cystitis cystica.

DIAGNOSIS

Cystitis cystica lends itself to diagnosis easily by cystoscopy. Identification of cysts in the mucous membrane of the upper urinary tract by urography is more difficult, and O'Flynn (1950) estimated that up to 1948 in only 32 cases had the diagnosis been established clinically. The lesions are more easily visualized by retrograde than intravenous pyelography. Dilatation of the ends of the minor calices with narrowing of the arms of the calix below, and cystic dilatation of the pelvi-ureteric junction are described (Hinman and Cordonnier, 1935), but the characteristic finding is the presence of multiple rounded filling defects in the pelvis and ureter. When numerous, these give rise to a frothy or bubbly appearance, and they are easily mistaken for air bubbles accidentally introduced during retrograde injection. It is necessary, therefore, to employ a technique of catheterization and injection which precludes the admission of air. The ureter often appears dilated and tortuous.

TREATMENT

Therapy should be directed to eradication of the primary cause, and renal infection and calculi treated by appropriate measures. There is no specific treatment for the cysts lining the pelvis and ureter, and as in the majority of cases they are probably not responsible for symptoms, none is required. Ureteric catheterization and instillation of 2 per cent silver nitrate solution is said to have reduced the number of cysts (Kindall, 1933). In unilateral cases where the associated kidney is non-functioning, nephrectomy is advisable. Although there is much evidence pointing to a relationship between cystitis cystica and carcinoma of the bladder, the author has been unable to find anything to suggest that a direct relationship exists between cystic changes in the upper urinary tract and malignancy. In choosing treatment, therefore, this factor can be left out of consideration. On the other hand an open mind should be kept on this subject—3 out of the 7 reported cases of pyelitis glandularis also had carcinoma (Plaut, 1939; Ackerman, 1946; Aiken, 1955), and pyelitis glandularis and pyelitis cystica are closely related conditions.

CASE HISTORY

A woman of 54 was seen in May, 1954, with a six-year history of urinary trouble. She complained of frequency, urgency, and scalding micturition, the symptoms coming on in attacks which lasted for a few weeks at a time. The frequency was not severe, and she only rose twice during the night. There had been no hæmaturia. She also complained of aching pain in the lower abdomen and back. The right kidney was palpable on physical examination.

A *catheter specimen of urine* contained a few pus cells and *B. coli* was cultured. At *cystoscopy* a number of small yellow vesicles were observed in the mucous membrane, grouped mostly around the left ureteric orifice, which was somewhat smaller than its fellow.

An *intravenous pyelogram* showed normal appearances on the right side except for a little dilatation of the ureter. The renal outline on the left side was small and there was very little evidence of secretion. One film showed evidence of dye outlining a small pelvis.

A *left retrograde pyelogram* confirmed the small atrophic character of the pelvis and calices, and also demonstrated the presence of multiple rounded filling defects in the pelvis and along the whole course of the ureter (*Fig.* 124).

A diagnosis of chronic pyelonephritis of the left kidney with grossly impaired function and associated pyelo-ureteritis and cystitis cystica was made, and a left nephrectomy advised. The patient's blood-pressure was within normal limits.

AT OPERATION.—A small adherent fibrotic left kidney was delivered and removed. The ureter was about twice the normal diameter, and was followed to the pelvic brim and divided there. On opening the pelvis and ureter the lining mucosa was seen to be studded with small rounded cysts containing yellow fluid (*Fig.* 125).

An uninterrupted recovery followed the operation, and the patient claims relief from her symptoms. A right ureterogram was subsequently carried out to exclude cystic changes on this side, but no such appearances were found.

PATHOLOGY.—Dr. MacCullagh Wilson reported on the histological appearances as follows: "The renal parenchyma is almost completely destroyed by a severe

FIG. 124.—Retrograde pyelogram showing multiple small rounded filling defects in the pelvis and ureter.

chronic pyelonephritis. The features of pyelitis and ureteritis cystica are present to a striking degree; the lining epithelium of some of the pelvic cysts has developed to cubical or low columnar type, and there is some evidence of mucus secretion, so that the condition approaches pyelitis glandularis."

Comment.—The case is an example of pyelitis and ureteritis cystica with similar, though less well-marked changes in the bladder, due to irritation associated with a longstanding and severe pyelonephritis of the related kidney. It makes an addition to the small number of cases which have been diagnosed by pyelographic methods. No calculi were present in this case, and the stimulus to metaplasia was provided by chronic infection alone. The localization of the cystic change to the pelvis and ureter draining the diseased kidney and the area of bladder mucosa around the corresponding ureteric orifice is striking. The observation on microscopical

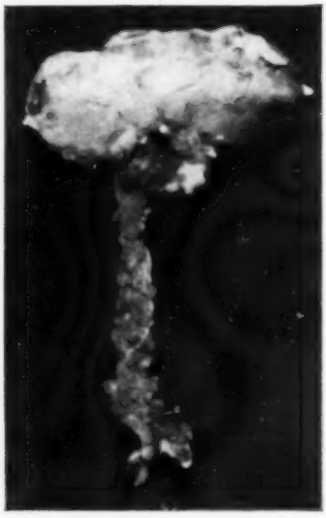

FIG. 125.—The operation specimen with the pelvis and ureter opened to show the mucosa studded with small cysts.

examination of early glandular changes in the epithelium is of special interest, and supports the view that is gaining ground, that pyelitis glandularis and pyelitis cystica are closely related, and represent different degrees of metaplasia in response to the same stimuli.

SUMMARY

1. The clinical and pathological features of pyelo-ureteritis cystica are briefly described.

2. An example of this condition secondary to chronic pyelonephritis is presented.

My thanks are due to Dr. W. C. MacCullagh Wilson for the histological report; to Dr. J. E. Glasgow for the radiological examinations; and to Mr. P. H. Partridge for the photographs of the specimen.

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COLLOID CYST OF THE PITUITARY GLAND CAUSING CHIASMAL COMPRESSION

By G. F. ROWBOTHAM and P. R. R. CLARKE

FROM THE REGIONAL CENTRE OF NEUROLOGICAL SURGERY, GENERAL HOSPITAL, NEWCASTLE UPON TYNE

THIS case is recorded because of its rarity. To our knowledge, no colloid cyst of the pituitary gland large enough to cause compression of the chiasma has previously been reported in the British literature.

CASE REPORT

A woman, aged 51, was referred to the Neurosurgical Unit in October, 1954. The history was that since 1929 she had suffered from partial amblyopia of the right eye due to a high refractive error. Early in 1953 she noticed that the vision in the left eye had deteriorated and, in August, 1954, the visual acuity on that side had dropped to 6/36 without, however, definite changes in the visual field. In October, 1954, examination on the perimeter and the Bjerrum screen showed that bitemporal hemianopia was developing, the changes being most marked in the areas of macular vision and in the upper peripheral quadrant on the left side (*Fig.* 126). Pallor of the left optic disk was also noted. Lateral radiography of the skull (*Fig.* 127) demonstrated displacement of the attenuated dorsum sellæ upwards and backwards, the floor of the sella turcica and the anterior clinoid processes being within normal limits. A diagnosis of expanding intrasellar lesion was made and it was decided that operative treatment was indicated.

AT OPERATION (Nov. 1, 1954).—A right frontal flap was raised and the dura mater was opened. On exposure of the right optic nerve a large cystic swelling rising out of the pituitary fossa could be seen beneath the optic chiasma. As attempts to aspirate the contents of the cyst with a syringe and wide-bore needle were unsuccessful, a vertical incision was made through the cyst wall. Following this a large quantity of extremely thick gelatinous material flowed slowly through the opening. The swelling then collapsed completely, relieving the pressure on the chiasma. The bone flap was replaced and the scalp reformed in layers.

Examination of the contents of the cyst showed that it consisted of structureless hyaline material in which were papillary tufts covered by cubical epithelium.

Post-operative progress was uneventful and when the patient was last seen in July, 1955, there had been no further deterioration of the visual acuity. The visual fields had not changed in character since the operation.

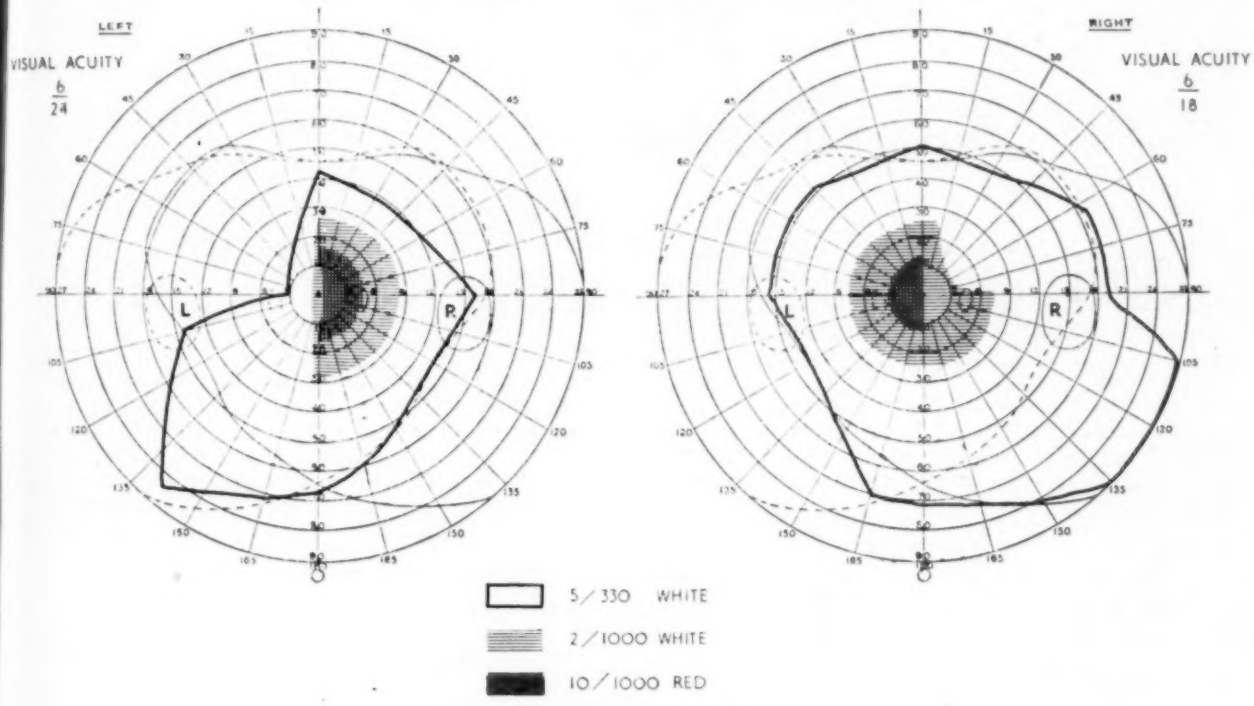

FIG. 126.—The visual fields before operation.

DISCUSSION

The pre-operative discovery of bitemporal visual field defect, affecting principally the inner isopters, suggested compression of the central area of the chiasma from below. This fact, together with the radiological picture and the operative findings, pointed to an intrasellar origin of the cyst. Although the eosinophil and chromophobe adenomata of the pituitary gland frequently undergo cystic degeneration, they do not form large colloid cysts and we feel that they can be excluded from the differential diagnosis in this case. Mucocele of the sphenoidal air sinus could present a similar picture, but radiologically and at operation the sella did not appear to be in communication with any of the paranasal

sinuses. Craniopharyngioma can also be eliminated in that the swelling was entirely intrasellar: there was no abnormal calcification to be seen on X-ray examination, and no cholesterol crystals were found in the cyst. Finally, the nature of the cyst contents is against a diagnosis of pituitary necrosis where the fluid is of a creamy consistency. We consider the most likely site of origin of the cyst in this case to be the hypophysial duct. Mucoid epithelial cysts of this structure are usually small, lined by ciliated epithelial cells and filled with mucus and cellular debris (Bailey, 1932).

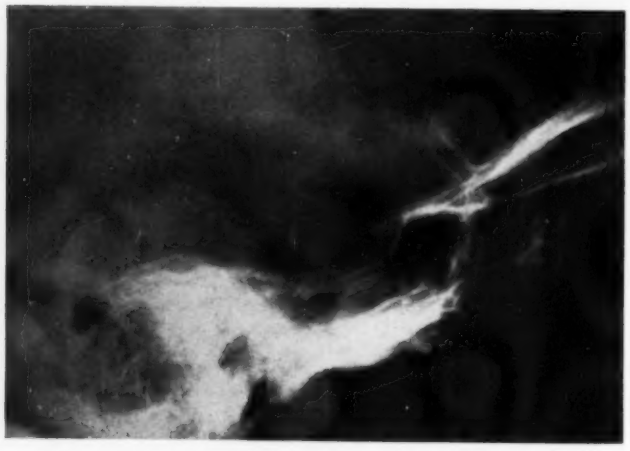

FIG. 127.—Lateral radiograph of the pituitary fossa illustrating the features mentioned in the text.

It is unlikely that the progressive pressure on the chiasma in this case could have been relieved other than by surgical means and it is considered that the transfrontal approach provided the best means of access to the swelling.

SUMMARY

A case of bitemporal hemianopia resulting from chiasmal compression by a colloid cyst of the pituitary gland is described and the opinion put forward that the cyst arose from the hypophysial duct.

We wish to express our thanks to Mr. J. S. Arkle for referring the case and for providing the ophthalmological details.

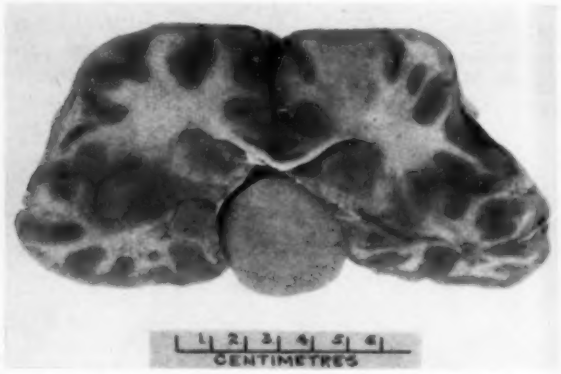

FIG. 128.—Extra-ventricular cyst found at post-mortem examination.

Addendum.—Since writing the above we have traced the notes of a previous case of extra-ventricular colloid cyst causing compression of the optic chiasma (*Fig.* 128). This specimen was found at a coroner's post-mortem examination in 1946 by Dr. G. E. Stephenson. The late Professor A. F. Bernard Shaw reported that there was a smooth rounded mass, measuring 4 × 3·5 × 3 cm. attached to the tuber cinereum. No trace of the pituitary gland or of its stalk could be found. Histologically, the cyst was lined by a layer of cuboidal cells and was filled with colloid. Professor Shaw thought it possible that the cyst was derived from the ependymal prolongation of the third ventricle into the infundibulum.

REFERENCE

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REVIEWS AND NOTICES OF BOOKS

The Casualty Department. By T. G. LOWDEN, M.A., B.M., B.Ch., F.R.C.S., Consultant Surgeon, Sunderland Royal Infirmary. 9⅝ × 6¾ in. Pp. 278 + viii, with 134 illustrations. 1955. Edinburgh: E. & S. Livingstone Ltd. 37s. 6d.

THE author dedicated this book to seventeen House Surgeons; no names are given but if these are those who have been attached to his Unit throughout the years, it is clear after perusal of the book that they must have other reasons for gratitude besides being mentioned. They will, no doubt, all have received a duly inscribed presentation copy, which to them will not only remind them of their 'old' chief but also of the care with which he taught them the precepts enshrined in the book. "It is the view of the writer that every case however 'minor' or trivial, demands a precise assessment from the casualty officer of what he hopes to achieve by administration of an antibiotic and that no 'new' antibiotic should be used if an 'older' one may be expected to act as effectively." Antibiotics are not intended to make it *easier* for the surgeon. They are intended to make it *better* for him. It is becoming fashionable that a new 'instrument,' the 'penicillin umbrella,' is used for every surgical procedure —just in case!

The Casualty Room in every hospital is a source of many headaches suffered not only by the Hospital Management Committee, Administrative Officers, and Consultant Staff, but also by all who have pride in the good reputation of the hospital. It is, by and large, the most important department in a hospital and it is for this reason, as it is beneath the dignity of the newly qualified to work in it, that a definite appointment in the department is a necessary antecedent before a candidate can present himself for a higher surgical diploma. The importance is such that a special grade of Senior Casualty Officer has been evolved in the National Health Service. Some Boards of Governors of Teaching Hospitals have gone even further and appointed Consultants who confine

themselves to the Casualty Department. The corollary is that a few observation beds should be attached to every casualty department, into which patients might be admitted and still be under the care of whoever is in charge of the department, with proper consultant cover, either owing to uncertainty in diagnosis, or for medical or medico-social reasons for a period of say forty-eight hours. If hospital treatment or observation is still necessary at the end of the period they would then be admitted to the wards under the consultant in charge.

The book deals only with soft-tissue injuries, fractures from the area served being admitted into a separate fracture and accident hospital.

The book is divided into three portions, the first dealing with the results and treatment of acute infections, the second describes the treatment of lesions in which acute infections play a very small part, and the third with the peculiar responsibility of the department both to certain aspects of medicine and surgery, the hospital as a whole, and in particular to the patient and the casualty officer.

In the first part stress is laid upon the principles of treating and preventing acute infection and especially so by adequate rest to the part and the use of the ideal dressing for a wound which is *skin*. The subsequent chapters in sequence deal with the closed and then the open soft-tissue injuries with either a mere breach of the cutaneous surface or definite skin deficiency. There is a very adequate chapter on the treatment of burns and scalds, and a most important one on anæsthesia in the casualty room. This latter chapter should be read and pondered over by all working in the department, who may thereby be made to realize that there is no such thing as a 'simple anæsthetic,' for at any time a minor procedure may become a major responsibility.

There is a tendency for the organization and work in the Casualty Department to remain static; innovations are frowned upon by the permanent officials; perhaps a similar state of affairs is the case in government offices, or so it seems to many. The new boy has to accept what was good enough for his predecessors back even for a generation; ritual tends to become routine.

The illustrations are excellent, but that is now expected in books sponsored by the publishers. The case histories illustrate the point which the author wishes to impress on his reader better than any illustration. The author is very right when he says: "The Casualty Department is not a place where careless and unsurgical habits may be indulged. It is the purpose of this book to show that precision in operating, precision in diagnosis, and precision in mental processes are inseparable from good results." The book demands a place in every hospital library.

Operative Technic in Specialty Surgery. Edited by WARREN H. COLE, M.D., F.A.C.S., Professor of Surgery and Head of the Department, University of Illinois College of Medicine. Second edition. 9½ × 6½ in. Pp. 967 + xxvi, with numerous illustrations. 1956. New York: Appleton-Century-Crofts Inc. $20.00.

THE second edition of this well-known American work has been very considerably revised, and Professor Warren Cole and his seventy-six contributing authors are to be congratulated upon producing such an interesting and very practical volume.

In this volume of nearly a thousand pages are included cardiovascular, thoracic, orthopædic, gynæcological, and neuro- and urological surgery. In every one of these special branches of surgery much new matter has been forthcoming in the last six years following the publication of the first edition. The greatest change may be found in the material on cardiovascular surgery, which has developed tremendously.

This work portrays the operative technique in use in American surgery to-day. It should prove of real value as a reference volume.

The Body Fluids. Basic Physiology and Practical Therapeutics. By J. RUSSELL ELKINGTON, M.D., Associate Professor of Medicine, University of Pennsylvania School of Medicine; and T. S. DANOWSKI, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine. 9 × 6 in. Pp. 626 + xxii, with 175 illustrations. 1956. London: Baillière, Tindall & Cox Ltd. 80s.

NEVER before in the history of medical science has the importance of body fluid dynamics been realized as it is to-day. The modern clinician must have a considerable knowledge of applied physiology and biochemistry, yet he cannot be expected to carry the up-to-date chemical information in his head and he must use the services of the medical biochemist.

This monograph will supply a great need and it should prove of real value to the clinician who wishes to know more of the concepts of physiology and biochemistry. The assessment of fluid disturbances and replacement therapy are of vital importance to-day.

An important reference volume for the modern surgeon.

Surgical Diagnosis. By PHILIP THOREK, M.D., F.A.C.S., F.I.C.S., Professor of Surgery, Cook County School of Medicine; etc. With drawings by CARL T. LINDEN, Assistant Professor of Medical Illustration, University of Illinois College of Medicine. 10 × 7 in. Pp. 320 + xii, with 291 illustrations. 1956. Philadelphia and Montreal: J. B. Lippincott Co. (London: Pitman Medical Publishing Co. Ltd.). 96s.

THIS is an illustrated monograph dealing with surgical diagnosis. The author is to be congratulated on the many and various ingenious drawings which illustrate the numerous signs which are of importance in the diagnosis of surgical conditions. If seeing is believing this book should certainly be popular with the modern medical students, who find the curriculum far too long and overcrowded these days.

Books of the simplicity of this one are rare to-day. It is refreshing to see something new appearing in what is an overcrowded field. One can learn more from a good picture than from many pages of the printed word.

An excellent book.

Peripheral Vascular Disorders. Edited by PETER MARTIN, V.R.D., M.Chir., F.R.C.S. (Edin)., Lecturer in Surgery, Postgraduate Medical School, London; R. BEVERLEY LYNN, M.D., F.R.C.S., Assistant Professor of Surgery and Markle Scholar, Medical College, University of Saskatchewan; J. HENRY DIBLE, M.B., LL.D., F.R.C.P., Professor Emeritus of Pathology, University of London; and IAN AIRD, Ch.M., F.R.C.S., Professor of Surgery, University of London; Director of Surgery, Postgraduate Medical School, London. 9¾ × 6¾ in. Pp. 847 + viii, with 450 illustrations. 1956. Edinburgh: E. & S. Livingstone. £5 10s.

THIS is a comprehensive work covering the whole field of peripheral vascular disorders; it is the work of a team working for the most part at the Postgraduate Hospital, Hammersmith. Professor G. A. C. Mitchell deals in a very interesting and practical manner with the innervation of the peripheral blood-vessels and treats the reader to some excellent original illustrations. This section of the book alone will prove of immense value to

the surgeon who has to operate on vascular disorders of the limbs.

Professor Henry Barcroft gives a very full survey of the physiology of blood-flow in the limbs.

Professor Ian Aird writes authoritatively on the treatment of embolism of the peripheral vessels, while Professor Henry Dible deals with the pathology of atherosclerosis.

Other sections of the book are devoted to radiology, surgery, and arterial trauma of the peripheral vessels. Lymphœdema and varicose veins are dealt with in a very practical way.

The whole work is extensively illustrated with excellent clinical photographs, photomicrographs, and radiographs. Each section has a large number of up-to-date references which should help anyone interested in any particular aspect of this large subject.

The whole volume is beautifully produced and there can be little doubt that it will become the standard book of reference on peripheral vascular disorders.

An Atlas illustrating the Topographical Anatomy of the Head, Neck, and Trunk. By the late JOHNSON SYMINGTON, M.D., F.R.C.S., F.R.S., Professor of Anatomy, The Queen's University, Belfast. 12 × 19 in. 34 plates on loose cards in cloth-bound holder. 1956. Edinburgh: Oliver & Boyd. £5 5s.

THIS Atlas contains 34 detached plates of 36 life-size horizontal sections through the head, neck, thorax, abdomen, and pelvis, with 7 reconstructions, also life-size. The plates are enclosed in a portfolio from which they can be taken and arranged conveniently for the comparison of adjacent sections. All the sections are viewed from above. The reconstructions show the position of the planes of sections and the thickness of the intervening slabs, and their relations of the skeleton and other structures.

This atlas is reprinted from the original atlas which was published in 1917 and is now published for the Anatomical Society of Great Britain and Ireland.

Few anatomical schools have serial sections of the human body on view in their museums and this composite atlas will fill a great need in the teaching of anatomy to-day.

Professor Symington is remembered not only as a distinguished anatomist but also as a great benefactor to the Anatomical Society. His name is commemorated in the Symington Prize, awarded at intervals of about three years for the best original work carried out by a junior member of the Society, and in the Symington Bequest, the residue of his estate, left to the Society by his daughter in 1932. As part of the estate the copyright of the "Atlas" and the original copper plates became the property of the Society.

The decision to reprint the "Atlas" was taken by the Council of the Society in 1954, and what a wise decision this was, for it has meant that this excellent atlas is now available to all anatomists, and clinical teachers, and will be much valued by a host of interested research workers.

The Boke of Chyldren. By THOMAS PHAIRE (1510–1560). Edited by A. V. NEALE, M.D., Professor Child Health, University of Bristol; and HUGH R. E. WALLIS, M.D., Consultant Pædiatrician, Bath Clinical Area. 7¼ × 4¾ in. Pp. 76, with 3 illustrations. 1955. Edinburgh: E. & S. Livingstone Ltd. 7s. 6d.

THIS book is dedicated by the Editors to Thomas Phaire (*circa* 1510–1560) and George Frederick Still (1868–1941) who was Physician to The Children's Hospital, Great Ormonde Street, and described the disease named after him in 1896.

Thomas Phaire published this, the first book on pædiatrics to be written by an Englishman, in 1545; it is also one of the earliest medical books to be printed in the English language. "George Frederick Still gave to the profession and to the world his famous book *The History of Pædiatrics* in 1931."

In 1929 George Still delivered the Fitzpatrick Lectures on Medical History at the Royal College of Physicians, London, and it was from the preparation of these that the idea originated of expanding them to form his classic on the history of pædiatrics. It was also from the Fitzpatrick Lectures delivered by Clifford Allbutt in 1909 that the profession gained another historical classic, namely *Greek Medicine in Rome*. Both these books approach their subject from the standpoint of "original sources, growths, movements of ideas and indeed their conflicts" rather than the purely biographical point of view. Be that as it may! Still was evidently as interested in Phaire's book as are the editors of this small duplicate copy of the original. He devoted a whole chapter in his History to a consideration of *The Boke of Chyldren* and its author, the main points of which, as the editors record, are given in their introduction to this edition. "This publication is an exact copy of a specimen of the 1553 edition which is in the Medical Library of the University of Bristol, England," which is also fortunate in possessing another copy of a later edition.

The publication of medical books in the vernacular language was the result of the Renaissance, which, by the publication of the book by Vesalius and the one by Copernicus, heralded the release of medicine from the authority and tradition of scholasticism. *The Boke of Chyldren* (1545), and that by Thomas Vicary *A Profitable Treatise of the Anatomie of Man's Body* (1548), illustrate this emancipation. Phaire "passes briefly over the management of the new born, choice of nurse, and suckling" but does refer to the condition of the mother's milk and the remedies for increasing it in quality and quantity. He then passes on to a consideration of the various problems met with by a pædiatrician such as teething, convulsions, nightmares, feeding, vomiting, infectious diseases, and cough, etc. The editors quote the original preface written by Phaire and end with a glossary explaining the medical terms used, the nature of the remedies advised, and the authors quoted.

This labour of love and reverence should make all present and future pædiatricians indebted to the editors and should persuade them to study the history of their specialty and especially the classic on this subject which was written by George Frederick Still.

Textbook of British Surgery. Edited by Sir HENRY SOUTTAR, C.B.E., D.M. (Oxon.), F.R.C.S., Consulting Surgeon, the London Hospital. 9¾ × 7⅜ in. Volume I, The Abdomen. Pp. 547 + viii, with 238 illustrations. 1956. London: William Heinemann Medical Books Ltd. 105s.

IT is given to few surgeons to edit a new work on surgery in their 81st year and we congratulate Sir Henry Souttar on no mean attainment.

The first volume of this new text-book of British surgery is devoted to "The Abdomen"; and has been contributed by fourteen surgeons, all of whom have written on subjects which they have made particularly their own. These contributors have been drawn from the leading medical schools and hospitals throughout the Kingdom. The volume is profusely illustrated with many original drawings, all of which are well chosen and help to enhance the text.

This first volume covers a general surgery of the abdomen: anatomy, injuries, stomach, duodenum, liver, gall-bladder, pancreas, portal hypertension, peritoneoscopy, appendix, Crohn's disease, diseases of the colon, rectum, and anus.

While all the contributions are excellent and criticism is not required and comparisons may be invidious, yet two sections of the volume stand out for sheer merit—namely, Mr. Lockhart-Mummery's chapter on the colon and Mr. Henry Thompson's chapter on the rectum and anus.

This volume should be of real value to the general surgeon, the senior registrar, and the countless post-graduates both at home and abroad who are reading for the Fellowship of the College of Surgeons.

This is a work of which British surgeons may well be proud.

The Year Book of Orthopedics and Traumatic Surgery, 1954–1955. Edited by EDWARD L. COMPERE, M.D., F.A.C.S., F.I.C.S., Professor and Chairman, Department of Bone and Joint Surgery, Northwestern University Medical School; etc. 7½ × 5¼ in. Pp. 384, with 193 illustrations. 1955. Chicago: Year Book Publishers Inc. (London: Interscience Publishers Ltd.). 45s.

THIS further issue is as valuable as its predecessors and the articles abstracted have been chosen with the discrimination we have come to expect from Dr. Compere. There are no startling innovations, but useful small advances all along the line which should be known to all orthopædic surgeons. As surgical literature becomes more and more voluminous the value of these year books increases correspondingly, though the period of gestation is of necessity about eighteen months.

Sir William Arbuthnot Lane, Bt., C.B., M.S. An Enquiry into the Mind and Influence of a Surgeon. By T. B. LAYTON, D.S.O., M.S., F.R.C.S. (Eng.), Consulting Surgeon Emeritus (Ear and Throat), Guy's Hospital, London. 8¾ × 6¼ in. Pp. 128 + viii, with 8 illustrations. 1956. Edinburgh: E. & S. Livingstone Ltd. 21s.

THIS is a colourful biography by one of Lane's former house surgeons and it gives the reader some idea of the surgical conditions which prevailed in the early nineties until after the first world war.

Arbuthnot Lane was certainly a unique surgeon who created a method and technique which is used to-day by many surgeons. While some operations devised by Lane may not be performed nowadays, yet they stand out as milestones in the long road of surgical advance. It is a pity perhaps that Lane was not more academic in his outlook; if he had been he would have been a very great man.

Mr. Layton has presented the surgical world with a fascinating book which will be greatly appreciated both at home and in the Americas.

The Cellular Basis of Wound Repair. By MARTIN ALLGÖWER, M.D., Privatdocent, Department of Surgery, University of Basle, Switzerland. 10 × 7 in. Pp. 125 + viii, with 45 illustrations. 1956. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell.) 47s. 6d.

THE repair of wounds is of interest not only to the surgeon but also to the pathologist and general practitioner, and much has been learnt about healing processes during the last decade. Professor Allgöwer in this monograph has attempted to re-establish the facts postulated long ago by A. Maximow that repair as regards regeneration of connective tissue finds principal support from an adequate local supply of mononuclear blood elements.

Many interesting facts concerning mitotic activity and concentration of cells are discussed. Skin-tissue cultures have been used to test for the presence of irradiation toxins in the serum of irradiated animals.

This book should prove an incentive to stimulate further interest for investigation of the theoretical aspect for repair which has lain dormant too long.

Tumors of the Skin. By HERBERT CONWAY, M.S., M.D., F.A.C.S., Professor of Clinical Surgery, Cornell University Medical College. 10 × 7 in. Pp. 267 + xiv, with 178 illustrations. 1956. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell Scientific Publications.) 97s.

THIS monograph comprises a series of lectures by Professor Conway given to medical students in the Department of Surgery, Cornell University Medical College over a period of twenty years. It is very comprehensive and covers the whole range of tumours which occur in the skin.

It is divided into two major sections, the first dealing with benign tumours of the skin; cysts, sinuses, fistulæ, and foreign body tumours. The second larger section is devoted to malignant tumours of the skin.

Throughout the book many excellent photographs help to enhance the value of the text—the photomicrographs are especially good. It is only when one reads a large monograph such as this that one realizes the variety and clinical appearances of tumours of the skin.

This book will remain for many years a reference volume dealing with the subject of skin tumours. It will not only prove of value to the surgeon and dermatologist but will also interest pathologists and senior students who wish to become *au fait* with this subject.

The Diagnosis and Management of Urological Cases. By BRUCE W. T. PENDER, M.B., B.S., F.R.C.S., and JAMES O. ROBINSON, M.A. (Cantab.), M. Chir., F.R.C.S. 8 × 5⅛ in. Pp. 170 + x, with 48 illustrations and 2 plates. 1955. London: Baillière, Tindall & Cox. 21s.

IT is a comment on the quality of the modern Senior Surgical Registrar that two of them should have written a book of this excellence. It is clear, concise, adequately illustrated, eminently practical, and easily read. For the student it will supplement the somewhat outdated accounts of urology given in many text-books on general surgery. For the house surgeon with the care of urological cases it will prove a very present help in trouble, and for the general practitioner a good revision course. We can recommend it warmly.

Practical Urology. Case Comments and Late Results. By ALEX. E. ROCHE, M.A., M.D., M.Ch. (Camb.), F.R.C.S. (Eng.), Genito-urinary Surgeon, West London, Royal Northern, and Hounslow Hospitals. 8½ × 5½ in. Pp. 258 + xii, with 132 illustrations. 1956. London: H. K. Lewis & Co. 35s.

FROM time to time there appears in *Punch* an article forming one of a series of "Misleading Cases". This book has something in common with that collection, although the most misleading part is its title. It is not a manual of urological procedures, but a series of case reports collected over a period of twenty-five years and presented with the wit and wisdom for which the author is justly renowned. Perhaps urology is a branch of surgery in which bizarre cases are common, or perhaps Mr. Roche has the facility for collecting such cases. His comments on each history usually point a moral.

It is characteristic that he does not spare himself in recounting omissions or mistakes, and even when critical of radiological reports he finds some word of sympathy or praise for the radiologist.

Despite the widespread use of abbreviations the matter is eminently readable. The terse phrase emphasizes essentials; "O.E. Shirt wet" is an example of the economy of words of which the author is a master.

There must be some criticism of over-conservatism in the treatment of enlarged prostate; the five criteria demanded before operation is permitted would by most urologists be considered signs of delay.

In general, however, the lessons are sound and orthodox and obviously influenced by the views of the more senior teachers.

This is an ideal bedside book which combines instruction with entertainment.

Thiopentone and Other Thiobarbiturates. By JOHN W. DUNDEE, M.D., F.F.A.R.C.S., D.A., Lecturer in Anæsthesia, University of Liverpool. 8½ × 5½ in. Pp. 312 + viii, with 59 illustrations. 1956. Edinburgh: E. & S. Livingstone Ltd. 22s. 6d.

THIS excellent text-book will appeal to a wide variety of readers. The first part deals with the history of intravenous anæsthesia and then continues with a most detailed pharmacology of the thiobarbiturates in general. The author has gone to very considerable trouble to consult all the experimental work which has been done on these substances, and the text is well illustrated by figures and graphs. Frequently the author has been able to draw from his own experience to confirm the work of other investigators, and this section will serve as a very fine work of reference for anyone interested in the thiobarbiturates.

The second part deals with the clinical use of these drugs and anæsthetists will find very little in what the author says with which to disagree. Once again the points he raises are well illustrated by case notes.

There is a small section which will be of interest to the occasional anæsthetist who wishes to use these drugs, in which the author gives very clear guidance as to their limitations and warning of their dangers. Finally, there is a small but very informative section dealing with syringe maintenance and intravenous equipment generally, and also a most useful list of intravenous drugs used in anæsthesia, giving details of their compatibility with each other. The bibliography is exhaustive, the work is well indexed, and the book is printed in the excellent manner which one has come to expect from E. & S. Livingstone Ltd.

As the author states in his preface, "For more than a decade there has been no publication devoted to these agents, although it is in this period that most progress has been made". This text-book certainly fills this deficit in medical literature admirably.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

The Pathology and Surgery of the Veins of the Lower Limbs. By HAROLD DODD, Ch.M., F.R.C.S., Surgeon to St. Mary's Hospital; etc.; and FRANK B. COCKETT, M.S., F.R.C.S., Surgeon to St. Thomas's Hospital. With a Foreword by R. R. LINTON, M.D., Assistant Clinical Professor of Surgery, Harvard Medical School. 9¾ × 6¾ in. Pp. 462 + xii, with 313 illustrations. 1956. Edinburgh: E. & S. Livingstone Ltd. 65s.

Pulmonary Carcinoma. Pathogenesis, Diagnosis, and Treatment. Edited by EDGAR MAYER, M.D., and HERBERT C. MAIER, M.D. 9 × 6 in. Pp. 540 + xvi, with numerous illustrations. 1956. New York: New York University Press. (London: Pitman Medical Publishing Co. Ltd.) £6.

Diagnosis and Treatment of Vascular Disorders (Angiology). Edited by SAUL S. SAMUELS, A.M., M.D., F.A.C.A., F.A.C.C., Editor-in-chief, Angiology; President, Angiology Research Foundation; etc. 10 × 6⅞ in. Pp. 621 + x, with numerous illustrations. 1956. London: Baillière, Tindall & Cox. 128s.

Modern Gynæcology with Obstetrics for Nurses. By W. E. HECTOR, Principal Tutor, St. Bartholomew's Hospital, London; and JOHN HOWKINS, M.D., F.R.C.S., Assistant Gynæcologist and Obstetric Surgeon, St. Bartholomew's Hospital, London. 8½ × 5½ in. Pp. 275 + viii, with 99 illustrations 1956. 17s. 6d.

The Dental Treatment of Maxillo-facial Injuries. By Sir WILLIAM KELSEY FRY, C.B.E., M.D.S., D.Sc., F.R.C.S., F.D.S., Consulting Dental Surgeon to the Royal Air Force, the Ministry of Health, and the Institute of Dental Surgery; Consulting Dental Surgeon Emeritus to Guy's Hospital; and TERENCE WARD, M.B.E., F.D.S. R.C.S., L.R.C.P., L.R.C.S. (Edin.), Consulting Dental Surgeon to the British Army and Queen Victoria Hospital, East Grinstead. Second edition. 8¾ × 5¾ in. Pp. 372 + xii, with 383 illustrations. 1956. Oxford: Blackwell Scientific Publications. 47s. 6d.

Airborne Contagion and Air Hygiene. An Ecological Study of Droplet Infections. By WILLIAM FIRTH WELLS. 9¼ × 6 in. Pp. 423 + xxxii, with 81 illustrations, many as plates. 1955. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass. (Distributed in Great Britain by Geoffrey Cumberlege, Oxford University Press, London.) 48s.

Plastic Repair of Genito-urinary Defects. By GEORGE BANKOFF, M.B., D.Ch., F.R.C.S. (Edin.), F.R.F.P.S., Honorary Surgeon, Italian Hospital, London. 9 × 6 in. Pp. 355 + xviii, with 86 illustrations. 1956. London: Pitman Medical Publishing Co. Ltd. £5 5s.